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(54) Title: **ACYCLIC AND CYCLIC AMINE DERIVATIVES**

(57) Abstract: The present invention relates to acyclic and cyclic amine derivatives for treating or preventing neuronal damage associated with neurological diseases. The invention also provides compositions comprising the compounds of the present invention and methods of utilizing those compositions for treating or preventing neuronal damage.

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ACYCLIC AND CYCLIC AMINE DERIVATIVES

TECHNICAL FIELD OF THE INVENTION

The present invention relates to acyclic and
5 cyclic amine derivatives for treating or preventing
neuronal damage associated with neurological diseases.
The invention also provides compositions comprising the
compounds of the present invention and methods of
utilizing those compositions for treating or preventing
10 neuronal damage.

BACKGROUND OF THE INVENTION

Neurological diseases are associated with the
death of or injury to neuronal cells. Typical treatment
of neurological diseases involves drugs capable of
15 inhibiting neuronal cell death. A more recent approach
involves the promotion of nerve regeneration by promoting
neuronal growth.

Neuronal growth, which is critical for the
survival of neurons, is stimulated *in vitro* by nerve
20 growth factors (NGF). For example, Glial Cell
Line-Derived Neurotrophic Factor (GDNF) demonstrates
neurotrophic activity both, *in vivo* and *in vitro*, and is
currently being investigated for the treatment of
Parkinson's disease. Insulin and insulin-like growth
25 factors have been shown to stimulate growth of neurites
in rat pheochromocytoma PC12 cells and in cultured
sympathetic and sensory neurons [Recio-Pinto et al., J.
Neurosci., 6, pp. 1211-1219 (1986)]. Insulin and
insulin-like growth factors also stimulate the

regeneration of injured motor nerves *in vivo* and *in vitro* [Near et al., Proc. Natl. Acad. Sci., pp. 89, 11716-11720 (1992); and Edbladh et al., Brain Res., 641, pp. 76-82 (1994)]. Similarly, fibroblast growth factor (FGF) stimulates neural proliferation [D. Gospodarowicz et al., Cell Differ., 19, p. 1 (1986)] and growth [M. A. Walter et al., Lymphokine Cytokine Res., 12, p. 135 (1993)].

There are, however, several disadvantages associated with the use of nerve growth factors for treating neurological diseases. They do not readily cross the blood-brain barrier. They are unstable in plasma and they have poor drug delivery properties.

Recently, small molecules have been shown to stimulate neurite outgrowth *in vivo*. In individuals suffering from a neurological disease, this stimulation of neuronal growth protects neurons from further degeneration, and accelerates the regeneration of nerve cells. For example, estrogen has been shown to promote the growth of axons and dendrites, which are neurites sent out by nerve cells to communicate with each other in a developing or injured adult brain [(C. Dominique Toran-Allerand et al., J. Steroid Biochem. Mol. Biol., 56, pp. 169-78 (1996); and B. S. McEwen et al., Brain Res. Dev. Brain. Res., 87, pp. 91-95 (1995)]. The progress of Alzheimer's disease is slowed in women who take estrogen. Estrogen is hypothesized to complement NGF and other neurotrophins and thereby help neurons differentiate and survive.

Other target sites for the treatment of neurodegenerative disease are the immunophilin class of proteins. Immunophilins are a family of soluble proteins

that mediate the actions of immunosuppressant drugs such as cyclosporin A, FK506 and rapamycin. Of particular interest is the 12 kDa immunophilin, FK-506 binding protein (FKBP12). FKBP12 binds FK-506 and rapamycin, leading to an inhibition of T-cell activation and proliferation. Interestingly, the mechanism of action of FK-506 and rapamycin are different. For a review, see, S. H. Solomon et al., Nature Med., 1, pp. 32-37 (1995). It has been reported that compounds with an affinity for FKBP12 that inhibit that protein's rotomase activity possess nerve growth stimulatory activity. [Lyons et al., Proc. Natl. Acad. Sci. USA, 91, pp. 3191-3195 (1994)]. Many of these such compounds also have immunosuppressive activity.

FK506 (Tacrolimus) has been demonstrated to act synergistically with NGF in stimulating neurite outgrowth in PC12 cells as well as sensory ganglia [Lyons et al. (1994)]. This compound has also been shown to be neuroprotective in focal cerebral ischemia [J. Sharkey and S. P. Butcher, Nature, 371, pp. 336-339 (1994)] and to increase the rate of axonal regeneration in injured sciatic nerve [B. Gold et al., J. Neurosci., 15, pp. 7509-16 (1995)].

The use of immunosuppressive compounds, however, has drawbacks in that prolonged treatment with these compounds can cause nephrotoxicity [Kopp et al., J. Am. Soc. Nephrol., 1, p. 162 (1991)], neurological deficits [P.C. DeGroen et al., N. Eng. J. Med., 317, p. 861 (1987)] and vascular hypertension [Kahan et al., N. Eng. J. Med., 321, p. 1725 (1989)].

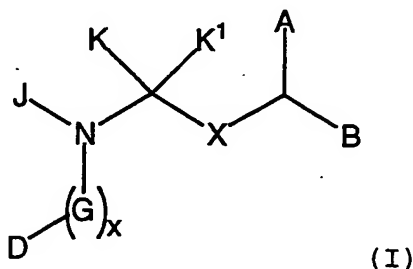
More recently, sub-classes of FKBP binding compounds which inhibit rotomase activity, but which purportedly lack immunosuppressive function have been disclosed for use in stimulating nerve growth [see, 5 United States patent 5,614,547; WO 96/40633; WO 96/40140; WO 97/16190; J. P. Steiner et al., Proc. Natl. Acad. Sci. USA , 94, pp. 2019-23 (1997); and G. S. Hamilton et al., Bioorg. Med. Chem. Lett., 7, pp. 1785-90 (1997)].

Stimulation of neural axons in nerve cells by 10 piperidine derivatives is described in WO 96/41609. Clinical use of the piperidine and pyrrolidine derivatives known so far for stimulating axonal growth has not been promising, as the compounds are unstable in plasma and do not pass the blood-brain barrier in 15 adequate amounts.

Though a wide variety of neurological degenerative diseases may be treated by promoting repair of neuronal damage, there are relatively few agents known to possess these properties. Thus, there remains a need 20 for new compounds and compositions that have the ability to either prevent or treat neuronal damage associated with neuropathologic disorders.

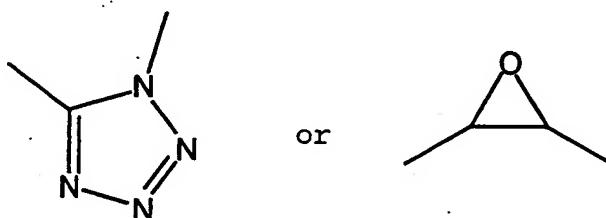
SUMMARY OF THE INVENTION

The invention provides compounds of formula 25 (I):



and pharmaceutically acceptable derivatives thereof,
wherein:

X is selected from $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{C}(\text{OH})\text{CH}_2-$,
 $-\text{CH}_2\text{C}(\text{OH})-$, $=\text{C}(\text{F})\text{CH}_2-$, $-\text{C}(\text{F})=\text{CH}_2-$, $-\text{NHC}(\text{O})-$, $-\text{P}(\text{O})(\text{OH})\text{CH}_2-$,
 5 $-\text{CH}_2\text{S}(\text{O})_2-$, $-\text{C}(\text{S})\text{NR}^1-$, $-\text{C}(\text{O})\text{CH}_2\text{CH}(\text{OH})-$, $-\text{C}(\text{OH})\text{CF}_2-$,
 $-\text{C}(\text{O})\text{CF}_2-$, $-\text{CH}(\text{F})\text{CH}_2-$, $-\text{C}(\text{F})_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{F})-$, $-\text{CH}_2\text{C}(\text{F})_2-$



A, B and R^1 are independently E, $(\text{C}_1-\text{C}_{10})$ -straight or
 branched alkyl, $(\text{C}_2-\text{C}_{10})$ -straight or branched alkenyl or
 10 alkynyl, or (C_5-C_7) -cycloalkyl or cycloalkenyl; wherein 1
 or 2 hydrogen atoms in said alkyl, alkenyl or alkynyl are
 optionally and independently replaced with E,
 (C_5-C_7) -cycloalkyl or cycloalkenyl; and wherein 1 to 2 of
 the $-\text{CH}_2-$ groups in said alkyl, alkenyl, or alkynyl groups
 15 is optionally and independently replaced by $-\text{O}-$, $-\text{S}-$,
 $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $=\text{N}-$, $-\text{N}=$ or $-\text{N}(\text{R}^3)-$;

or, B and R^1 are independently hydrogen;

R^3 is hydrogen, (C_1-C_4) -straight or branched alkyl,
 (C_3-C_4) -straight or branched alkenyl or alkynyl, or (C_1-C_4)
 20 bridging alkyl, wherein a bridge is formed between the
 nitrogen atom to which said R^3 is bound and any carbon
 atom of said alkyl, alkenyl or alkynyl to form a ring,
 and wherein said ring is optionally benzofused;

E is a saturated, partially saturated or
 25 unsaturated, or aromatic monocyclic or bicyclic ring
 system, wherein each ring comprises 5 to 7 ring atoms

independently selected from C, N, N(R³), O, S, S(O), or S(O)₂; and wherein no more than 4 ring atoms are selected from N, N(R³), O, S, S(O), or S(O)₂;

wherein 1 to 4 hydrogen atoms in E are optionally
5 and independently replaced with halogen, hydroxyl, hydroxymethyl, nitro, SO₃H, trifluoromethyl, trifluoromethoxy, (C₁-C₆)-straight or branched alkyl, (C₂-C₆)-straight or branched alkenyl, O-[(C₁-C₆)-straight or branched alkyl], O-[(C₃-C₆)-straight or branched
10 alkenyl], (CH₂)_n-N(R⁴)(R⁵), (CH₂)_n-NH(R⁴)-(CH₂)_n-Z, (CH₂)_n-N(R⁴-(CH₂)_n-Z)(R⁵-(CH₂)_n-Z), (CH₂)_n-Z, O-(CH₂)_n-Z, (CH₂)_n-O-Z, S-(CH₂)_n-Z, CH=CH-Z, 1,2-methylenedioxy, C(O)OH, C(O)O-[(C₁-C₆)-straight or branched alkyl], C(O)O-(CH₂)_n-Z or C(O)-N(R⁴)(R⁵);

15 each of R⁴ and R⁵ are independently hydrogen, (C₁-C₆)-straight or branched alkyl, (C₃-C₅)-straight or branched alkenyl, or wherein R⁴ and R⁵, when bound to the same nitrogen atom, are taken together with the nitrogen atom to form a 5 or 6 membered ring, wherein said ring
20 optionally contains 1 to 3 additional heteroatoms independently selected from N, N(R³), O, S, S(O), or S(O)₂; wherein said alkyl, alkenyl or alkynyl groups in R₄ and R₅ are optionally substituted with Z.

each n is independently 0 to 4;

25 each Z is independently selected from a saturated, partially saturated or unsaturated, monocyclic or bicyclic ring system, wherein each ring comprises 5 to 7 ring atoms independently selected from C, N, N(R³), O, S, S(O), or S(O)₂; and wherein no more than 4 ring atoms are
30 selected from N, N(R³), O, S, S(O), or S(O)₂;

wherein 1 to 4 hydrogen atoms in Z are optionally

and independently replaced with halo, hydroxy, nitro,
cyano, C(O)OH, (C₁-C₃)-straight or branched alkyl,
O-(C₁-C₃)-straight or branched alkyl,
C(O)O-[(C₁-C₃)-straight or branched alkyl], amino,
5 NH[(C₁-C₃)-straight or branched alkyl], or
N-[(C₁-C₃)-straight or branched alkyl]₂;

J is H, methyl, ethyl or benzyl;

K and K¹ are independently selected from
(C₁-C₆)-straight or branched alkyl, (C₂-C₆)-straight or
10 branched alkenyl or alkynyl, or cyclohexylmethyl, wherein
1 to 2 hydrogen atoms in said alkyl, alkenyl or alkynyl
is optionally and independently replaced with E;

wherein K and K¹ are independently and optionally
substituted with up to 3 substituents selected from
15 halogen, OH, O-(C₁-C₆)-alkyl, O-(CH₂)_n-Z, NO₂, C(O)OH,
C(O)-O-(C₁-C₆)-alkyl, C(O)NR⁴R⁵, NR⁴R⁵ and (CH₂)_n-Z; or,

J and K, taken together with the nitrogen and carbon
atom to which they are respectively bound, form a 5-7
membered heterocyclic ring, optionally containing up to 3
20 additional heteroatoms selected from N, N(R³), O, S, S(O),
or S(O)₂, wherein 1 to 4 hydrogen atoms in said
heterocyclic ring are optionally and independently
replaced with (C₁-C₆)-straight or branched alkyl,
(C₂-C₆)-straight or branched alkenyl or alkynyl, oxo,
25 hydroxyl or Z; and wherein any -CH₂- group in said alkyl,
alkenyl or alkynyl substituent is optionally and
independently replaced by -O-, -S-, -S(O)-, -S(O)₂-, =N-,
-N=, or -N(R³)-; and wherein said heterocyclic ring is
optionally fused with E;

30 G, when present, is -S(O)₂-, -C(O)-, -S(O)₂-Y-,
-C(O)-Y-, -C(O)-C(O)-, or -C(O)-C(O)-Y-;

Y is oxygen, or N(R⁶);

wherein R⁶ is hydrogen, E, (C₁-C₆)-straight or branched alkyl, (C₃-C₆)-straight or branched alkenyl or alkynyl; or wherein R⁶ and D are taken together with the
5 atoms to which they are bound to form a 5 to 7 membered ring system wherein said ring optionally contains 1 to 3 additional heteroatoms independently selected from O, S, N, N(R³), SO, or SO₂; and wherein said ring is optionally benzofused;

10 D is hydrogen, (C₁-C₇)-straight or branched alkyl, (C₂-C₇)-straight or branched alkenyl or alkynyl, (C₅-C₇)-cycloalkyl or cycloalkenyl optionally substituted with (C₁-C₆)-straight or branched alkyl or (C₂-C₇)-straight or branched alkenyl or alkynyl, [(C₁-C₇)-alkyl]-E,
15 [(C₂-C₇)-alkenyl or alkynyl]-E, or E;

wherein 1 to 2 of the CH₂ groups of said alkyl, alkenyl or alkynyl chains in D is optionally replaced by -O-, -S-, -S(O)-, -S(O)₂-, =N-, -N=, or -N(R³);

provided that when J is hydrogen or G is selected
20 from -S(O)₂-, C(O)C(O)-, SO₂-Y, C(O)-Y, or C(O)C(O)-Y, wherein Y is O; then D is not hydrogen; and

x is 0 or 1.

In another embodiment, the invention provides pharmaceutical compositions comprising the compounds of
25 formula (I). These compositions may be utilized in methods treating various neurological diseases which are influenced by neuronal regeneration and axon growth or for stimulating neuronal regeneration in an ex vivo nerve cell. Examples of such diseases include peripheral nerve
30 destruction due to physical injury or diseases such as diabetes; physical injuries to the central nervous system

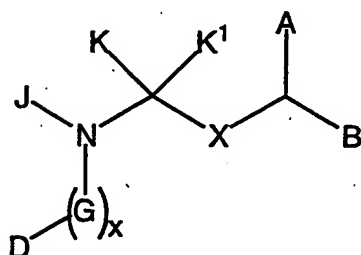
(e.g., brain or spinal cord); stroke; neurological disturbances due to nerve degeneration, such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis.

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DETAILED DESCRIPTION OF THE INVENTION

The invention provides compounds of formula

(I):

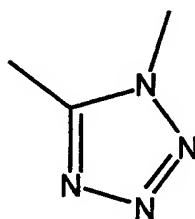


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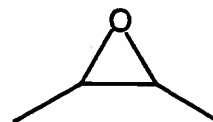
and pharmaceutically acceptable derivatives thereof,

10 wherein:

X is selected from $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{C}(\text{OH})\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{OH})-$, $=\text{C}(\text{F})\text{CH}_2-$, $-\text{C}(\text{F})=\text{CH}_2-$, $-\text{NHC}(\text{O})-$, $-\text{P}(\text{O})(\text{OH})\text{CH}_2-$, $-\text{CH}_2\text{S}(\text{O})_2-$, $-\text{C}(\text{S})\text{NR}^1-$, $-\text{C}(\text{O})\text{CH}_2\text{CH}(\text{OH})-$, $-\text{C}(\text{OH})\text{CF}_2-$, $-\text{C}(\text{O})\text{CF}_2-$, $-\text{CH}(\text{F})\text{CH}_2-$, $-\text{C}(\text{F})_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{F})-$, $-\text{CH}_2\text{C}(\text{F})_2-$,



or



15

A, B and R^1 are independently E, $(\text{C}_1-\text{C}_{10})$ -straight or branched alkyl, $(\text{C}_2-\text{C}_{10})$ -straight or branched alkenyl or alkynyl, or (C_5-C_7) -cycloalkyl or cycloalkenyl; wherein 1 or 2 hydrogen atoms in said alkyl, alkenyl or alkynyl are optionally and independently replaced with E, (C_5-C_7) -cycloalkyl or cycloalkenyl; and wherein 1 to 2 of the $-\text{CH}_2-$ groups in said alkyl, alkenyl, or alkynyl groups

20

-10-

is optionally and independently replaced by -O-, -S-,
-S(O)-, -S(O)₂-, =N-, -N= or -N(R³)-;

or, B and R¹ are independently hydrogen;

R³ is hydrogen, (C₁-C₄)-straight or branched alkyl,
5 (C₃-C₄)-straight or branched alkenyl or alkynyl, or (C₁-C₄)
bridging alkyl, wherein a bridge is formed between the
nitrogen atom to which said R³ is bound and any carbon
atom of said alkyl, alkenyl or alkynyl to form a ring,
and wherein said ring is optionally benzofused;

10 E is a saturated, partially saturated or
unsaturated, or aromatic monocyclic or bicyclic ring
system, wherein each ring comprises 5 to 7 ring atoms
independently selected from C, N, N(R³), O, S, S(O), or
S(O)₂; and wherein no more than 4 ring atoms are selected
15 from N, N(R³), O, S, S(O), or S(O)₂;

wherein 1 to 4 hydrogen atoms in E are optionally
and independently replaced with halogen, hydroxyl,
hydroxymethyl, nitro, SO₃H, trifluoromethyl,
trifluoromethoxy, (C₁-C₆)-straight or branched alkyl,
20 (C₂-C₆)-straight or branched alkenyl, O-[(C₁-C₆)-straight
or branched alkyl], O-[(C₃-C₆)-straight or branched
alkenyl], (CH₂)_n-N(R⁴)(R⁵), (CH₂)_n-NH(R⁴)-(CH₂)_n-Z,
(CH₂)_n-N(R⁴)-(CH₂)_n-Z (R⁵-(CH₂)_n-Z), (CH₂)_n-Z, O-(CH₂)_n-Z,
(CH₂)_n-O-Z, S-(CH₂)_n-Z, CH=CH-Z, 1,2-methylenedioxy,
25 C(O)OH, C(O)O-[(C₁-C₆)-straight or branched alkyl],
C(O)O-(CH₂)_n-Z or C(O)-N(R⁴)(R⁵);

each of R⁴ and R⁵ are independently hydrogen,
(C₁-C₆)-straight or branched alkyl, (C₃-C₅)-straight or
branched alkenyl, or wherein R⁴ and R⁵, when bound to the
30 same nitrogen atom, are taken together with the nitrogen
atom to form a 5 or 6 membered ring, wherein said ring

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optionally contains 1 to 3 additional heteroatoms independently selected from N, N(R³), O, S, S(O), or S(O)₂; wherein said alkyl, alkenyl or alkynyl groups in R₄ and R₅ are optionally substituted with Z.

5 each n is independently 0 to 4;

each Z is independently selected from a saturated, partially saturated or unsaturated, monocyclic or bicyclic ring system, wherein each ring comprises 5 to 7 ring atoms independently selected from C, N, N(R³), O, S, S(O), or S(O)₂; and wherein no more than 4 ring atoms are selected from N, N(R³), O, S, S(O), or S(O)₂;

wherein 1 to 4 hydrogen atoms in Z are optionally and independently replaced with halo, hydroxy, nitro, cyano, C(O)OH, (C₁-C₃)-straight or branched alkyl, O-(C₁-C₃)-straight or branched alkyl, C(O)O-[(C₁-C₃)-straight or branched alkyl], amino, NH[(C₁-C₃)-straight or branched alkyl], or N-[(C₁-C₃)-straight or branched alkyl]₂;

J is H, methyl, ethyl or benzyl;

20 K and K¹ are independently selected from (C₁-C₆)-straight or branched alkyl, (C₂-C₆)-straight or branched alkenyl or alkynyl, or cyclohexylmethyl, wherein 1 to 2 hydrogen atoms in said alkyl, alkenyl or alkynyl is optionally and independently replaced with E;

25 wherein K and K¹ are independently and optionally substituted with up to 3 substituents selected from halogen, OH, O-(C₁-C₆)-alkyl, O-(CH₂)_n-Z, NO₂, C(O)OH, C(O)-O-(C₁-C₆)-alkyl, C(O)NR⁴R⁵, NR⁴R⁵ and (CH₂)_n-Z; or,

J and K, taken together with the nitrogen and carbon atom to which they are respectively bound, form a 5-7 membered heterocyclic ring, optionally containing up to 3

additional heteroatoms selected from N, N(R³), O, S, S(O), or S(O)₂, wherein 1 to 4 hydrogen atoms in said heterocyclic ring are optionally and independently replaced with (C₁-C₆)-straight or branched alkyl, (C₂-C₆)-straight or branched alkenyl or alkynyl, oxo, hydroxyl or Z; and wherein any -CH₂- group in said alkyl, alkenyl or alkynyl substituent is optionally and independently replaced by -O-, -S-, -S(O)-, -S(O)₂-, =N-, -N=, or -N(R³)-; and wherein said heterocyclic ring is optionally fused with E;

G, when present, is -S(O)₂-, -C(O)-, -S(O)₂-Y-, -C(O)-Y-, -C(O)-C(O)-, or -C(O)-C(O)-Y-;

Y is oxygen, or N(R⁶);

wherein R⁶ is hydrogen, E, (C₁-C₆)-straight or branched alkyl, (C₃-C₆)-straight or branched alkenyl or alkynyl; or wherein R⁶ and D are taken together with the atoms to which they are bound to form a 5 to 7 membered ring system wherein said ring optionally contains 1 to 3 additional heteroatoms independently selected from O, S, N, N(R³), SO, or SO₂; and wherein said ring is optionally benzofused;

D is hydrogen, (C₁-C₇)-straight or branched alkyl, (C₂-C₇)-straight or branched alkenyl or alkynyl, (C₅-C₇)-cycloalkyl or cycloalkenyl optionally substituted with (C₁-C₆)-straight or branched alkyl or (C₂-C₇)-straight or branched alkenyl or alkynyl, [(C₁-C₇)-alkyl]-E, [(C₂-C₇)-alkenyl or alkynyl]-E, or E;

wherein 1 to 2 of the CH₂ groups of said alkyl, alkenyl or alkynyl chains in D is optionally replaced by -O-, -S-, -S(O)-, -S(O)₂-, =N-, -N=, or -N(R³);

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provided that when J is hydrogen or G is selected from $-S(O)_2-$, $C(O)C(O)-$, SO_2-Y , $C(O)-Y$, or $C(O)C(O)-Y$, wherein Y is O; then D is not hydrogen; and

x is 0 or 1.

5 According to a preferred embodiment, each of A and B in formula (I) is (C_1-C_{10}) straight or branched alkyl, wherein 1-2 hydrogen atoms in said alkyl are optionally substituted with E.

In another preferred embodiment, B is hydrogen.

10 According to another preferred embodiment, each of A and B in formula (I) is $-CH_2-CH_2-E$ or $-CH_2-CH_2-CH_2-E$.

 According to another preferred embodiment, D in formula (I) is (C_1-C_7) straight or branched alkyl, E or $[(C_1-C_6)\text{-straight or branched alkyl}]-E$.

15 According to a more preferred embodiment, D is an aromatic monocyclic or bicyclic ring system, wherein each ring comprises 5-7 ring atoms independently selected from C, N, O or S, and wherein no more than 4 ring atoms are selected from N, O or S.

20 According to an even more preferred embodiment, D is phenyl or C_1-C_7 straight or branched alkyl group.

 According to another preferred embodiment, E in formula (I) is a monocyclic or bicyclic aromatic ring system, wherein said ring comprises 5-7 ring atoms
25 independently selected from C, N, $N(R^3)$, O, S, $S(O)$, or $S(O)_2$, and wherein 1 to 4 ring atoms are independently selected from N, $N(R^3)$, O, S, $S(O)$, or $S(O)_2$.

 Preferred embodiments of E include phenyl,
naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl,
30 furyl, thienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl,

isothiazolyl, 1,3,4-thiadiazolyl, pyridazinyl,
pyrimidinyl, 1,3,5-triazinyl, 1,3,5-trithianyl,
benzo[b]furanyl, benzo[b]thiophenyl, purinyl, cinnolinyl,
phthalazinyl, isoxazolyl, triazolyl, oxadiazolyl,
5 pyrimidinyl, pyrazinyl, indolinyl, indolizinyl,
isoindolyl, benzimidazolyl, benzothiophenyl, quinolinyl,
isoquinolinyl, quinazolinyl, quinoxalinyl,
1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl,
phnazinyl, phenothiazinyl, phenoxazinyl and
10 benzothiazolyl, wherein E is optionally substituted as
described above.

More preferred embodiments of E include phenyl,
furyl, thienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl,
imidazolyl, pyrazolyl, isoxazolyl, triazolyl,
15 oxadiazolyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl,
benzimidazolyl, benzothiophenyl, quinolinyl,
isoquinolinyl, and benzothiazolyl, wherein E is
optionally substituted as described above.

According to another preferred embodiment, J is
20 H, methyl, ethyl or benzyl; and

K is selected from (C₁-C₆)-straight or branched
alkyl, (C₂-C₆)-straight or branched alkenyl or alkynyl, or
cyclohexylmethyl, wherein 1 to 2 hydrogen atoms in said
alkyl, alkenyl or alkynyl is optionally and independently
25 replaced with E.

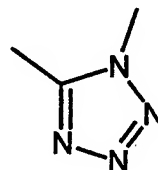
According to another preferred embodiment, J
and K, taken together with the nitrogen atom, form a 5-7
membered heterocyclic ring, optionally containing up to 3
additional heteroatoms selected from N, N(R³), O, S, S(O),
30 or S(O)₂, wherein 1 to 4 hydrogen atoms in said
heterocyclic ring are optionally and independently

-15-

replaced with (C₁-C₆)-straight or branched alkyl,
(C₂-C₆)-straight or branched alkenyl or alkynyl, oxo,
hydroxyl or Z; and wherein any -CH₂- group said
heterocyclic ring is optionally and independently
5 replaced by -O-, -S-, -S(O)-, -S(O₂)-, =N-, -N=, or
-N(R³)-; and wherein said heterocyclic ring is optionally
fused with E.

According to yet another preferred embodiment,
X is selected from -CH₂CH₂-, -CH=CH-, -C(OH)CH₂-,
10 -CH₂C(OH)-, -C(F)=CH₂-, -CH₂S(O)₂-, -C(S)NR¹-,
-C(O)CH₂CH(OH)-, -C(OH)CF₂-, -C(O)CF₂-, -CH(F)CH₂-,

-C(F)₂CH₂-, -CH₂CH(F)-, -CH₂C(F)₂-, or

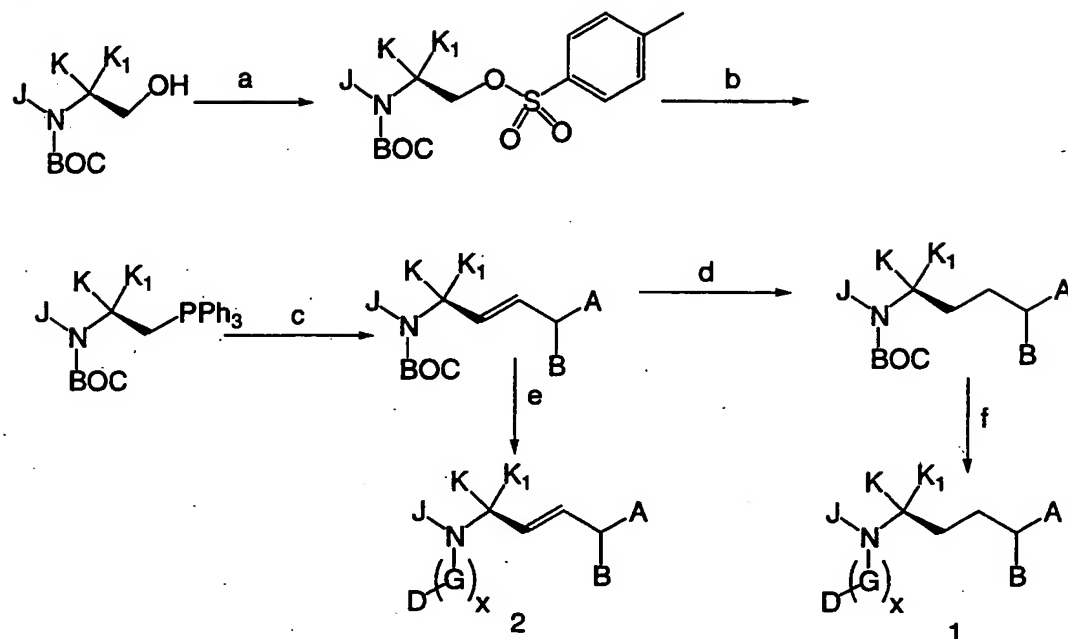


The compounds of formula (I) may be
stereoisomers, geometric isomers or stable tautomers.
15 The invention envisions all possible isomers, such as E
and Z isomers, S and R enantiomers, diastereoisomers,
racemates, and mixtures of those. It is preferred that
the substituent in the 2 position have the S
configuration.

20 The compounds of the present invention may be
readily prepared using known synthetic methods. For
synthetic methods for the preparation of X, which are
amide bond bioisosteres see: "Peptidomimetics Protocols"
in Methods on Molecular Medicine, Vol 30, 1999, Humana
25 Press, Totowa New Jersey, Kazmierski, W.M., Ed.

Examples of synthetic schemes that may be used
to produce the compounds of this invention are set forth
in Schemes 1 through 6 below.

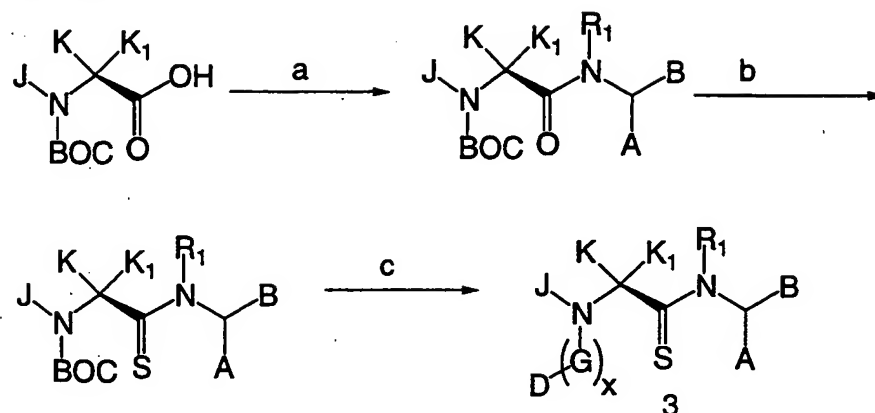
Scheme 1

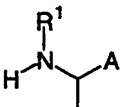


a = p-toluenesulfonyl chloride; diisopropylethylamine and CH_2Cl_2 ; b = NaI and acetone; followed by PPh_3 and

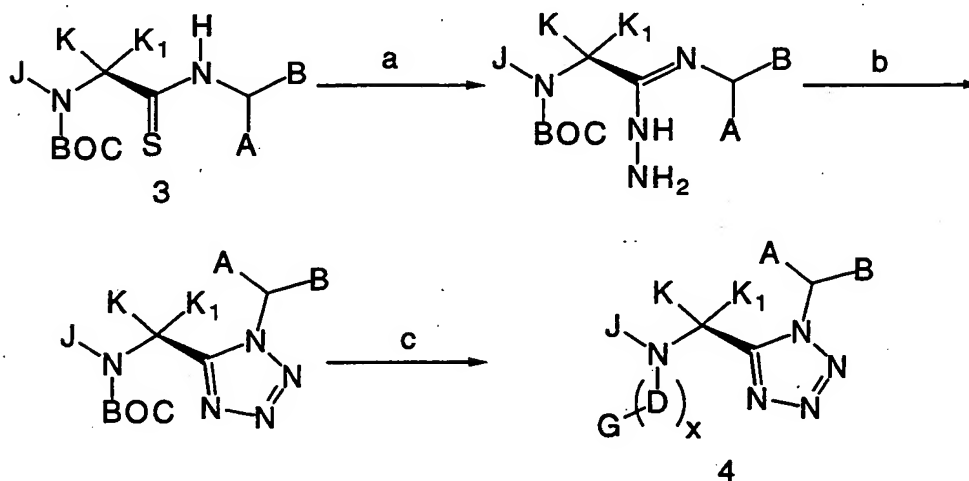
5 toluene; c = NaH, and THF; followed by $\text{H-C(=O)-CH}_2\text{-A}$; d = 10% Pd/C, H_2 gas, and MeOH; e = HCl(g)/ethyl acetate or TFA/dichloromethane; followed by $(\text{CH}_2)_x\text{-Br}$, K_2CO_3 and DMF if $(\text{G})_x = (\text{CH}_2)_x$; or D-C(O)-Cl, diisopropylethylamine, and CH_2Cl_2 if $(\text{G})_x = -\text{C(O)}$, wherein X is 0 or 1.

Scheme 2



- a = , HOBT, EDC, and CH₂Cl₂; b = Lawesson's reagent and toluene; c = HCl(g)/ethyl acetate or TFA/dichloromethane; followed by (CH₂)_x-Br, K₂CO₃ and DMF if (G)_x = (CH₂)_x; or D-C(O)-Cl, diisopropylethylamine, and CH₂Cl₂ if (G)_x = -C(O), wherein X is 0 or 1.
- 5
- 10

Scheme 3

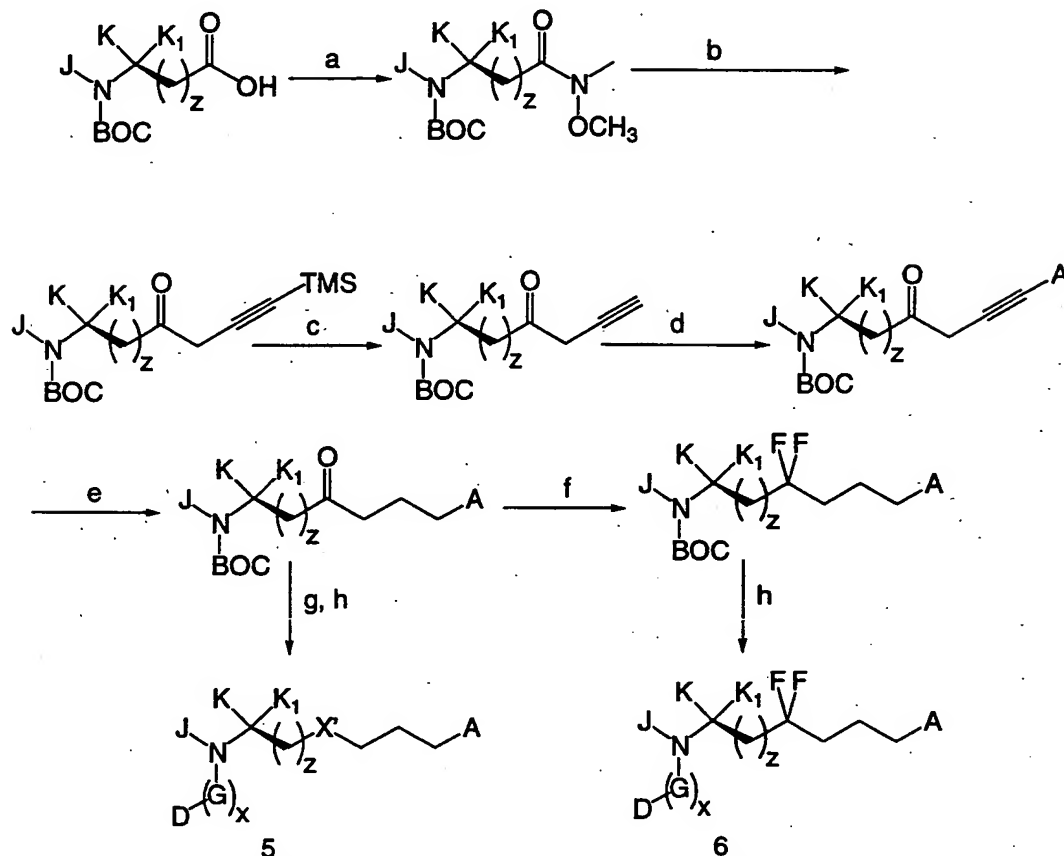


- a = H₂NNH₂·H₂O, and ethanol; b = NaNO₂, acetic acid, and H₂O; c = HCl(g)/ethyl acetate or TFA/dichloromethane; followed by (CH₂)_x-Br, K₂CO₃ and DMF if (G)_x = (CH₂)_x; or D-
- 15

C(O)-Cl, diisopropylethylamine, and CH₂Cl₂ if (G)_x = -C(O)-, wherein X is 0 or 1.

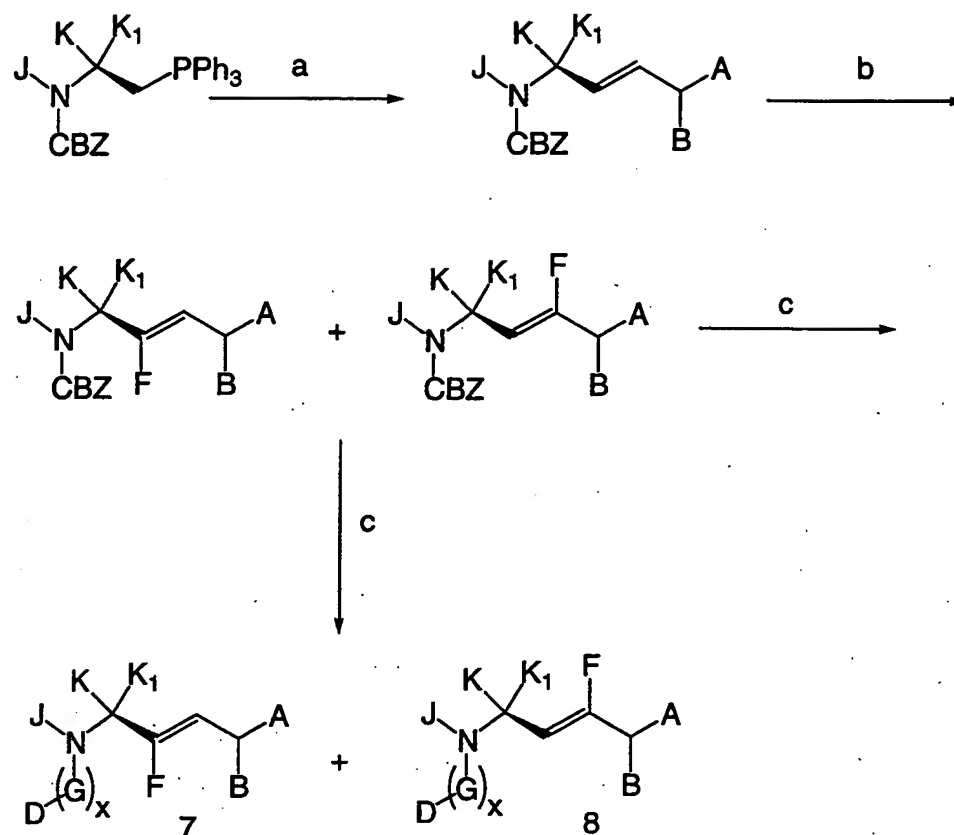
Scheme 4

5



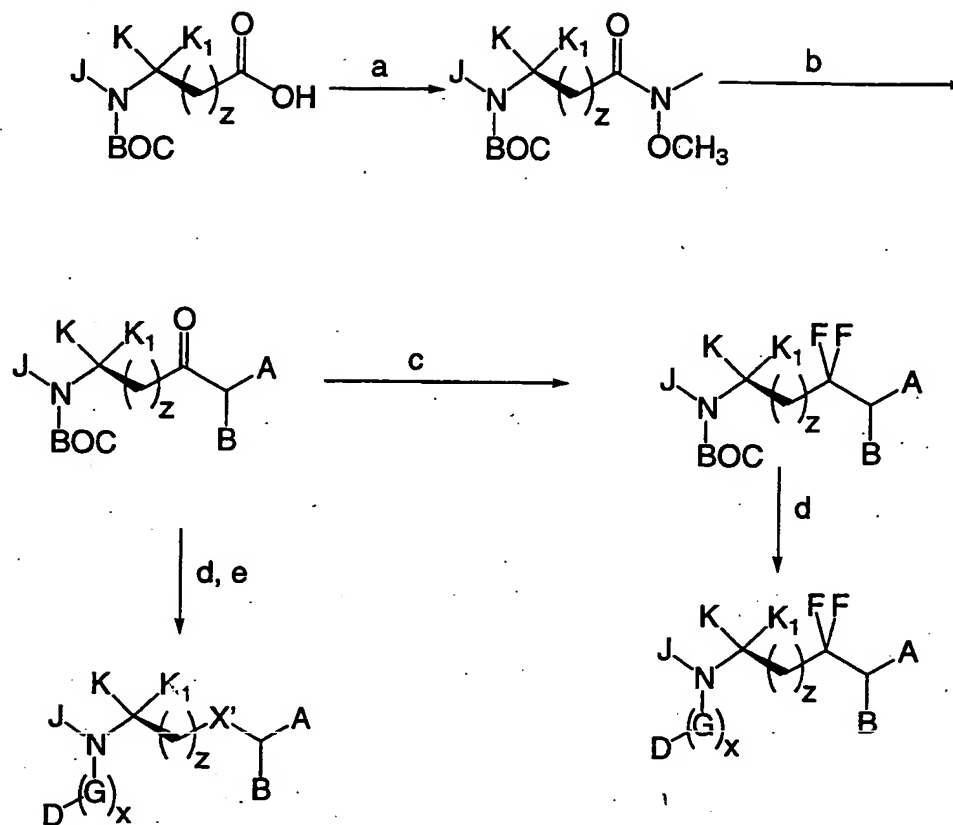
- a = N,O-dimethylhydroxylamine hydrochloride, EDC, diisopropylethylamine, and CH₂Cl₂; b = 3-(trimethylsilyl)propargyl magnesium bromide and THF; c = Bu₄NF/THF; d = aryl halide (Br or I), (Ph₃P)₄Pd(0), Et₃N, and THF; e = 5% Pd/C, H₂ (1 atm), and MeOH; f = Et₂N-SF₃, and CH₂Cl₂; g = NaBH₄, and MeOH, when X' = CH(OH) or DAST, and CH₂Cl₂, when X = CHF; h = HCl(g)/ethyl acetate or TFA/dichloromethane; followed by (CH₂)_x-Br, K₂CO₃ and DMF if (G)_x = (CH₂)_x; or D-C(O)-Cl, diisopropylethylamine, and CH₂Cl₂ if (G)_x = -C(O)-, wherein x is 0 or 1; z = 0 or 1; and X' = -C(O)-, -CH(OH)- or -CHF-.

Scheme 5

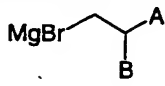


5
 a = NaH and THF; followed by aldehyde derivative; b =
 NBS, Bu₄NF/HF, and CH₂Cl₂; followed by KOtBu, and Et₂O; c =
 TMSI, and CH₃CN; followed by (CH₂)_x-Br, K₂CO₃ and DMF if
 (G)_x = (CH₂)_x; or D-C(O)-Cl, diisopropylethylamine, and
 10 CH₂Cl₂ if (G)_x = -C(O), wherein x is 0 or 1.

Scheme 6



a = N,O-dimethylhydroxylamine hydrochloride, EDC,

diisopropylethylamine, and CH₂Cl₂; b =  and THF;

- 5 c = Et₂N-SF₃, and CH₂Cl₂; d = NaBH₄, and MeOH, when X' = CH(OH), or DAST and CH₂Cl₂, when X = CHF; e = HCl(g)/ethyl acetate or TFA/dichloromethane; followed by (CH₂)_x-Br, K₂CO₃ and DMF if (G)_x = (CH₂)_x; or D-C(O)-Cl, diisopropylethylamine, and CH₂Cl₂ if (G)_x = -C(O)-, wherein
 10 x is 0 or 1; z = 0 or 1; and X' = -C(O)-, -CH(OH)- or -CHF-.

One of skill in the art will also be well aware of analogous synthetic methods for preparing compounds of
 15 formula (I).

According to another embodiment, this invention provides compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxy methylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

In another embodiment, the pharmaceutical composition of the present invention is comprised of a compound of formula (I), a pharmaceutically acceptable carrier, and a neurotrophic factor.

The term "neurotrophic factor," as used herein, refers to compounds which are capable of stimulating growth or proliferation of nervous tissue. Numerous neurotrophic factors have been identified in the art and any of those factors may be utilized in the compositions of this invention. These neurotrophic factors include, but are not limited to, nerve growth factor (NGF), insulin-like growth factor (IGF-1) and its active truncated derivatives such as gIGF-1 and Des(1-3)IGF-I, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived growth factors (PDGF), brain-derived neurotrophic factor (BDNF), ciliary

neurotrophic factors (CNTF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3) and neurotrophin 4/5 (NT-4/5). The most preferred neurotrophic factor in the compositions of this invention
5 is NGF.

As used herein, the described compounds used in the pharmaceutical compositions and methods of this invention, are defined to include pharmaceutically acceptable derivatives thereof. A "pharmaceutically
10 acceptable derivative" denotes any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this invention or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound of this invention, or
15 a metabolite or residue thereof, characterized by the ability to promote repair or prevent damage of neurons from disease or physical trauma.

If pharmaceutically acceptable salts of the described compounds are used, those salts are preferably
20 derived from inorganic or organic acids and bases. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate,
25 digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate,
30 oxalate, palmoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate,

succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

The described compounds utilized in the compositions and methods of this invention may also be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous,

intramuscular, intra-articular, intra-synovial,
intrasternal, intrathecal, intrahepatic, intralesional
and intracranial injection or infusion techniques.
Preferably, the compositions are administered orally,
5 intraperitoneally or intravenously.

Sterile injectable forms of the compositions of
this invention may be aqueous or oleaginous suspension.
These suspensions may be formulated according to
techniques known in the art using suitable dispersing or
10 wetting agents and suspending agents. The sterile
injectable preparation may also be a sterile injectable
solution or suspension in a non-toxic
parenterally-acceptable diluent or solvent, for example
as a solution in 1,3-butanediol. Among the acceptable
15 vehicles and solvents that may be employed are water,
Ringer's solution and isotonic sodium chloride solution.
In addition, sterile, fixed oils are conventionally
employed as a solvent or suspending medium. For this
purpose, any bland fixed oil may be employed including
20 synthetic mono- or di-glycerides. Fatty acids, such as
oleic acid and its glyceride derivatives are useful in
the preparation of injectables, as are natural
pharmaceutically-acceptable oils, such as olive oil or
castor oil, especially in their polyoxyethylated
25 versions. These oil solutions or suspensions may also
contain a long-chain alcohol diluent or dispersant, such
as Ph. Hely or similar alcohol.

The pharmaceutical compositions of this
invention may be orally administered in any orally
30 acceptable dosage form including, but not limited to,
capsules, tablets, aqueous suspensions or solutions. In

-25-

the case of tablets for oral use, carriers which are commonly used include lactose and corn starch.

Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule
5 form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

10 Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room
15 temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this
20 invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily
25 prepared for each of these areas or organs.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation.

Topically-transdermal patches may also be used.

30 For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment

containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid
5 petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or
10 dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

15 For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as
20 benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or
25 inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability,
30 fluorocarbons, and/or other conventional solubilizing or dispersing agents.

The amount of both a described compound and the optional neurotrophic factor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the described compound can be administered. If a neurotrophic factor is present in the composition, then a dosage of between 0.01 μ g - 100 mg/kg body weight/day of the neurotrophic factor can be administered to a patient receiving these compositions.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of active ingredients will also depend upon the particular described compound and neurotrophic factor in the composition.

According to another embodiment, this invention provides methods for promoting repair or preventing neuronal damage or neurodegeneration *in vivo* or in an *ex vivo* nerve cell. Such methods comprise the step of treating nerve cells with any of the compounds described above. Preferably, this method promotes repair or prevents neuronal damage or neurodegeneration in a patient, and the compound is formulated into a

composition additionally comprising a pharmaceutically acceptable carrier. The amount of the compound utilized in these methods is between about 0.01 and 100 mg/kg body weight/day.

5 According to an alternate embodiment, the method of promoting repair or preventing neuronal damage or neurodegeneration comprises the additional step of treating nerve cells with a neurotrophic factor, such as those contained in the pharmaceutical compositions of
10 this invention. This embodiment includes administering the compound and the neurotrophic agent in a single dosage form or in separate, multiple dosage forms. If separate dosage forms are utilized, they may be administered concurrently, consecutively or within less
15 than about 5 hours of one another.

 Preferably, the methods of this invention are used to stimulate axonal growth in nerve cells. The compounds are, therefore, suitable for treating or preventing neuronal damage caused by a wide variety of
20 diseases or physical traumas. These include, but are not limited to, Alzheimer's disease, Parkinson's disease, ALS, Huntington's disease, Tourette's syndrome, stroke and ischemia associated with stroke, neural paropathy, other neural degenerative diseases, motor neuron
25 diseases, sciatic crush, spinal cord injuries and facial nerve crush.

 In a particularly preferred embodiment of the invention, the method is used to treat a patient suffering from trigeminal neuralgia, glossopharyngeal
30 neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, muscle injury, progressive muscular atrophy,

progressive bulbar inherited muscular atrophy, herniated, ruptured, or prolapsed intervertebrae disk syndrome's, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies, such as
5 those caused by lead, dapsone, ticks, or porphyria, other peripheral myelin disorders, Alzheimer's disease, Gullain-Barre syndrome, Parkinson's disease and other Parkinsonian disorders, ALS, Tourette's syndrome, multiple sclerosis, other central myelin disorders,
10 stroke and ischemia associated with stroke, neural paropathy, other neural degenerative diseases, motor neuron diseases, sciatic crush, neuropathy associated with diabetes, spinal cord injuries, facial nerve crush and other trauma, chemotherapy- and other
15 medication-induced neuropathies, and Huntington's disease.

More preferably, the compositions of the present invention are used for treating Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's
20 disease, stroke, neuralgias, muscular atrophies, and Guillain-Barré syndrome.

For use of the compounds according to the invention as medications, they are administered in the form of a pharmaceutical preparation containing not only
25 the active ingredient but also carriers, auxiliary substances, and/or additives suitable for enteric or parenteral administration. Administration can be oral or sublingual as a solid in the form of capsules or tablets, as a liquid in the form of solutions, suspensions,
30 elixirs, aerosols or emulsions, or rectal in the form of suppositories, or in the form of solutions for injection

which can be given subcutaneously, intramuscularly, or intravenously, or which can be given topically or intrathecally. Auxiliary substances for the desired medicinal formulation include the inert organic and
5 inorganic carriers known to those skilled in the art, such as water, gelatin, gum arabic, lactose, starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, etc. The medicinal formulations may also contain preservatives, stabilizers, wetting agents,
10 emulsifiers, or salts to change the osmotic pressure or as buffers.

Solutions or suspensions for injection are suitable for parenteral administration, and especially aqueous solutions of the active compounds in
15 polyhydroxy-ethoxylated castor oil.

Surface-active auxiliary substances such as salts of gallic acid, animal or vegetable phospholipids, or mixtures of them, and liposomes or their components, can be used as carrier systems.

20 The neurotrophic effect of the compounds of formula (I) of the present invention and their physiologically acceptable salts can be determined by the methods of W. E. Lyons et al., Proc. Natl. Acad. Sci. USA, Vol. 91, pp. 3191-3195 (1994) and W. E. Lyons et
25 al., Proc. Natl. Acad. Sci. USA, Vol. 91, pages 3191-3195 (1994), the disclosures of which are herein incorporated by reference.

In order that this invention be more fully understood, the following examples are set forth. These
30 examples are for the purpose of illustration only and are

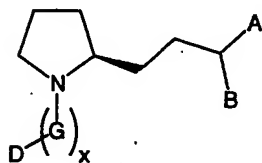
not to be construed as limiting the scope of the invention in any way.

EXAMPLE 1

Compounds 100-295


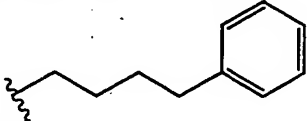
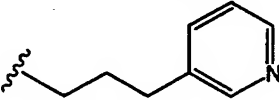
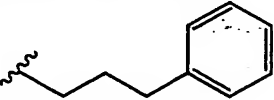
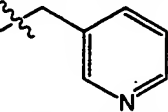
- 5 Compounds 101-296 are synthesized via the method set forth in Scheme 1, above. In all of the examples, "Ph" is phenyl.

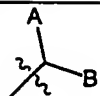
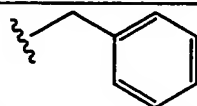
Compounds 100-148 have the formula:



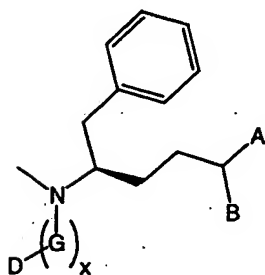
- 10 , with the individual variables defined in the table below.

| Cmpd # | A B | - (G) _x -D |
|--------|---------------|----------------------------------|
| 100 | | -CH ₃ |
| 101 | Same as above | -CH ₂ CH ₃ |
| 102 | Same as above | -C(=O)-CH ₃ |
| 103 | Same as above | -CH ₂ -Ph |
| 104 | Same as above | -C(=O)-Ph |
| 105 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 106 | Same as above | -C(=O)-C(=O)-Ph |
| 107 | | -CH ₃ |
| 108 | Same as above | -CH ₂ CH ₃ |

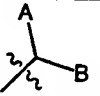
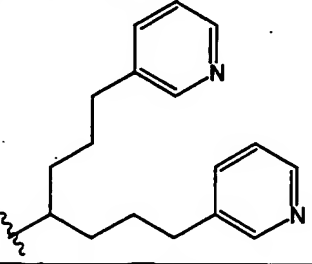
| Cmpd # |  | $-(G)_x-D$ |
|--------|-------------------------------------------------------------------------------------|--------------------|
| 109 | Same as above | $-C(=O)-CH_3$ |
| 110 | Same as above | $-CH_2-Ph$ |
| 111 | Same as above | $-C(=O)-Ph$ |
| 112 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 113 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 114 |  | $-CH_3$ |
| 115 | Same as above | $-CH_2CH_3$ |
| 116 | Same as above | $-C(=O)-CH_3$ |
| 117 | Same as above | $-CH_2-Ph$ |
| 118 | Same as above | $-C(=O)-Ph$ |
| 119 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 120 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 121 |  | $-CH_3$ |
| 122 | Same as above | $-CH_2CH_3$ |
| 123 | Same as above | $-C(=O)-CH_3$ |
| 124 | Same as above | $-CH_2-Ph$ |
| 125 | Same as above | $-C(=O)-Ph$ |
| 126 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 127 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 128 |  | $-CH_3$ |
| 129 | Same as above | $-CH_2CH_3$ |
| 130 | Same as above | $-C(=O)-CH_3$ |
| 131 | Same as above | $-CH_2-Ph$ |
| 132 | Same as above | $-C(=O)-Ph$ |
| 133 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 134 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 135 |  | $-CH_3$ |
| 136 | Same as above | $-CH_2CH_3$ |
| 137 | Same as above | $-C(=O)-CH_3$ |
| 138 | Same as above | $-CH_2-Ph$ |
| 139 | Same as above | $-C(=O)-Ph$ |
| 140 | Same as above | $-C(=O)-O-CH_2-Ph$ |


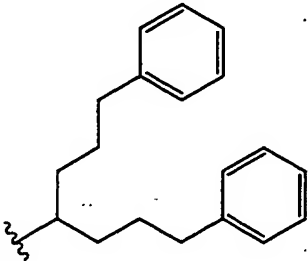
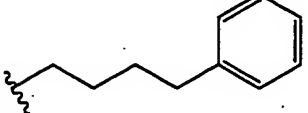
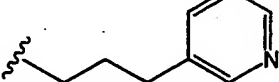
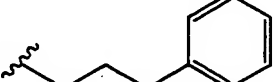
| Cmpd # |  | $-(G)_x-D$ |
|--------|-----------------------------------------------------------------------------------|--------------------|
| 141 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 142 |  | $-CH_3$ |
| 143 | Same as above | $-CH_2CH_3$ |
| 144 | Same as above | $-C(=O)-CH_3$ |
| 145 | Same as above | $-CH_2-Ph$ |
| 146 | Same as above | $-C(=O)-Ph$ |
| 147 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 148 | Same as above | $-C(=O)-C(=O)-Ph$ |


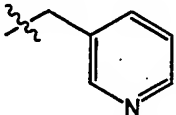
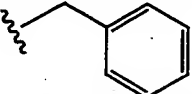
Compounds 149-197 have the formula:



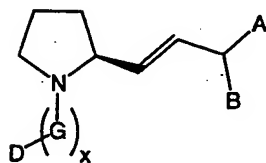
5 the table below. , with the individual variables defined in

| Cmpd # |  | $-(G)_x-D$ |
|--------|-------------------------------------------------------------------------------------|--------------------|
| 149 |  | $-CH_3$ |
| 150 | Same as above | $-CH_2CH_3$ |
| 151 | Same as above | $-C(=O)-CH_3$ |
| 152 | Same as above | $-CH_2-Ph$ |
| 153 | Same as above | $-C(=O)-Ph$ |
| 154 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 155 | Same as above | $-C(=O)-C(=O)-Ph$ |


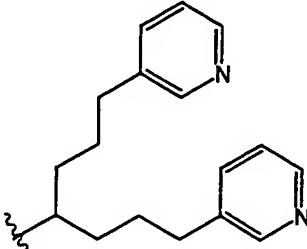
| Cmpd # |  | - (G) _x -D |
|------------|-------------------------------------------------------------------------------------|----------------------------------|
| 156 |  | -CH ₃ |
| 157 | Same as above | -CH ₂ CH ₃ |
| 158 | Same as above | -C(=O)-CH ₃ |
| 159 | Same as above | -CH ₂ -Ph |
| 160 | Same as above | -C(=O)-Ph |
| 161 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 162 | Same as above | -C(=O)-C(=O)-Ph |
| 163 |  | -CH ₃ |
| 164 | Same as above | -CH ₂ CH ₃ |
| 165 | Same as above | -C(=O)-CH ₃ |
| 166 | Same as above | -CH ₂ -Ph |
| 167 | Same as above | -C(=O)-Ph |
| 168 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 169 | Same as above | -C(=O)-C(=O)-Ph |
| 170 |  | -CH ₃ |
| 171 | Same as above | -CH ₂ CH ₃ |
| 172 | Same as above | -C(=O)-CH ₃ |
| 173 | Same as above | -CH ₂ -Ph |
| 174 | Same as above | -C(=O)-Ph |
| 175 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 176 | Same as above | -C(=O)-C(=O)-Ph |
| 177 |  | -CH ₃ |
| 178 | Same as above | -CH ₂ CH ₃ |
| 179 | Same as above | -C(=O)-CH ₃ |
| 180 | Same as above | -CH ₂ -Ph |
| 181 | Same as above | -C(=O)-Ph |
| 182 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 183 | Same as above | -C(=O)-C(=O)-Ph |

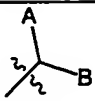
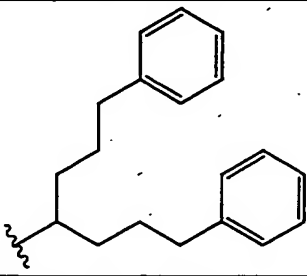
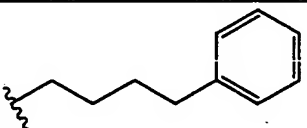
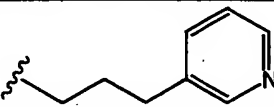
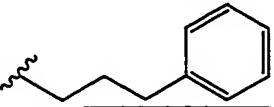
| Cmpd # |  | $-(G)_x-D$ |
|--------|-----------------------------------------------------------------------------------|--------------------|
| 184 |  | $-CH_3$ |
| 185 | Same as above | $-CH_2CH_3$ |
| 186 | Same as above | $-C(=O)-CH_3$ |
| 187 | Same as above | $-CH_2-Ph$ |
| 188 | Same as above | $-C(=O)-Ph$ |
| 189 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 190 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 191 |  | $-CH_3$ |
| 192 | Same as above | $-CH_2CH_3$ |
| 193 | Same as above | $-C(=O)-CH_3$ |
| 194 | Same as above | $-CH_2-Ph$ |
| 195 | Same as above | $-C(=O)-Ph$ |
| 196 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 197 | Same as above | $-C(=O)-C(=O)-Ph$ |

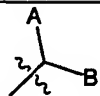
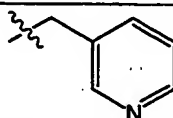
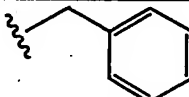
Compounds 198-246 have the formula:



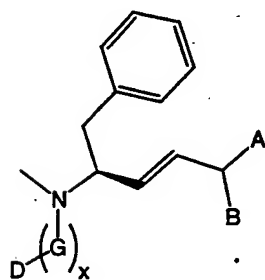
5 , with the individual variables defined in the table below.

| Cmpd # |  | $-(G)_x-D$ |
|--------|-------------------------------------------------------------------------------------|---------------|
| 198 |  | $-CH_3$ |
| 199 | Same as above | $-CH_2CH_3$ |
| 200 | Same as above | $-C(=O)-CH_3$ |

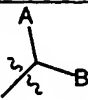
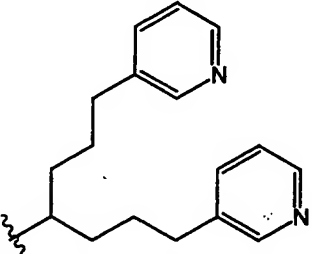
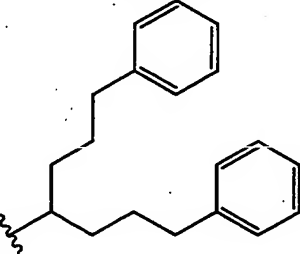
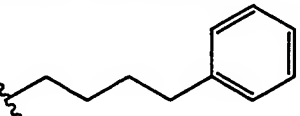
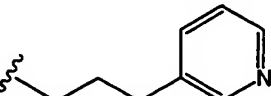
| Cmpd # |  | $-(G)_x-D$ |
|--------|-------------------------------------------------------------------------------------|--------------------|
| 201 | Same as above | $-CH_2-Ph$ |
| 202 | Same as above | $-C(=O)-Ph$ |
| 203 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 204 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 205 |  | $-CH_3$ |
| 206 | Same as above | $-CH_2CH_3$ |
| 207 | Same as above | $-C(=O)-CH_3$ |
| 208 | Same as above | $-CH_2-Ph$ |
| 209 | Same as above | $-C(=O)-Ph$ |
| 210 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 211 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 212 |  | $-CH_3$ |
| 213 | Same as above | $-CH_2CH_3$ |
| 214 | Same as above | $-C(=O)-CH_3$ |
| 215 | Same as above | $-CH_2-Ph$ |
| 216 | Same as above | $-C(=O)-Ph$ |
| 217 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 218 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 219 |  | $-CH_3$ |
| 220 | Same as above | $-CH_2CH_3$ |
| 221 | Same as above | $-C(=O)-CH_3$ |
| 222 | Same as above | $-CH_2-Ph$ |
| 223 | Same as above | $-C(=O)-Ph$ |
| 224 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 225 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 226 |  | $-CH_3$ |
| 227 | Same as above | $-CH_2CH_3$ |
| 228 | Same as above | $-C(=O)-CH_3$ |

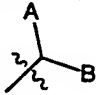
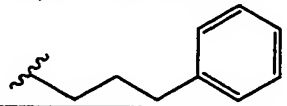
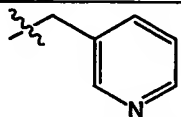
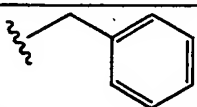
| Compd # |  | $-(G)_x-D$ |
|---------|-----------------------------------------------------------------------------------|--------------------|
| 229 | Same as above | $-CH_2-Ph$ |
| 230 | Same as above | $-C(=O)-Ph$ |
| 231 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 232 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 233 |  | $-CH_3$ |
| 234 | Same as above | $-CH_2CH_3$ |
| 235 | Same as above | $-C(=O)-CH_3$ |
| 236 | Same as above | $-CH_2-Ph$ |
| 237 | Same as above | $-C(=O)-Ph$ |
| 238 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 239 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 240 |  | $-CH_3$ |
| 241 | Same as above | $-CH_2CH_3$ |
| 242 | Same as above | $-C(=O)-CH_3$ |
| 243 | Same as above | $-CH_2-Ph$ |
| 244 | Same as above | $-C(=O)-Ph$ |
| 245 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 246 | Same as above | $-C(=O)-C(=O)-Ph$ |

Compounds 247-295 have the formula:



5 , with the individual variables defined in the table below.

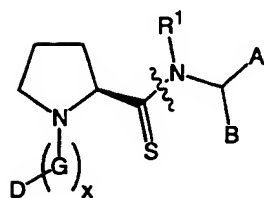
| Cmpd # |  | - (G) _x -D |
|--------|-------------------------------------------------------------------------------------|----------------------------------|
| 247 |  | -CH ₃ |
| 248 | Same as above | -CH ₂ CH ₃ |
| 249 | Same as above | -C(=O)-CH ₃ |
| 250 | Same as above | -CH ₂ -Ph |
| 251 | Same as above | -C(=O)-Ph |
| 252 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 253 | Same as above | -C(=O)-C(=O)-Ph |
| 254 |  | -CH ₃ |
| 255 | Same as above | -CH ₂ CH ₃ |
| 256 | Same as above | -C(=O)-CH ₃ |
| 257 | Same as above | -CH ₂ -Ph |
| 258 | Same as above | -C(=O)-Ph |
| 259 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 260 | Same as above | -C(=O)-C(=O)-Ph |
| 261 |  | -CH ₃ |
| 262 | Same as above | -CH ₂ CH ₃ |
| 263 | Same as above | -C(=O)-CH ₃ |
| 264 | Same as above | -CH ₂ -Ph |
| 265 | Same as above | -C(=O)-Ph |
| 266 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 267 | Same as above | -C(=O)-C(=O)-Ph |
| 268 |  | -CH ₃ |

| Cmpd # |  | $-(G)_x-D$ |
|--------|-------------------------------------------------------------------------------------|-------------------------------------------------------|
| 269 | Same as above | $-\text{CH}_2\text{CH}_3$ |
| 270 | Same as above | $-\text{C}(=\text{O})-\text{CH}_3$ |
| 271 | Same as above | $-\text{CH}_2-\text{Ph}$ |
| 272 | Same as above | $-\text{C}(=\text{O})-\text{Ph}$ |
| 273 | Same as above | $-\text{C}(=\text{O})-\text{O}-\text{CH}_2-\text{Ph}$ |
| 274 | Same as above | $-\text{C}(=\text{O})-\text{C}(=\text{O})-\text{Ph}$ |
| 275 |  | $-\text{CH}_3$ |
| 276 | Same as above | $-\text{CH}_2\text{CH}_3$ |
| 277 | Same as above | $-\text{C}(=\text{O})-\text{CH}_3$ |
| 278 | Same as above | $-\text{CH}_2-\text{Ph}$ |
| 279 | Same as above | $-\text{C}(=\text{O})-\text{Ph}$ |
| 280 | Same as above | $-\text{C}(=\text{O})-\text{O}-\text{CH}_2-\text{Ph}$ |
| 281 | Same as above | $-\text{C}(=\text{O})-\text{C}(=\text{O})-\text{Ph}$ |
| 282 |  | $-\text{CH}_3$ |
| 283 | Same as above | $-\text{CH}_2\text{CH}_3$ |
| 284 | Same as above | $-\text{C}(=\text{O})-\text{CH}_3$ |
| 285 | Same as above | $-\text{CH}_2-\text{Ph}$ |
| 286 | Same as above | $-\text{C}(=\text{O})-\text{Ph}$ |
| 287 | Same as above | $-\text{C}(=\text{O})-\text{O}-\text{CH}_2-\text{Ph}$ |
| 288 | Same as above | $-\text{C}(=\text{O})-\text{C}(=\text{O})-\text{Ph}$ |
| 289 |  | $-\text{CH}_3$ |
| 290 | Same as above | $-\text{CH}_2\text{CH}_3$ |
| 291 | Same as above | $-\text{C}(=\text{O})-\text{CH}_3$ |
| 292 | Same as above | $-\text{CH}_2-\text{Ph}$ |
| 293 | Same as above | $-\text{C}(=\text{O})-\text{Ph}$ |
| 294 | Same as above | $-\text{C}(=\text{O})-\text{O}-\text{CH}_2-\text{Ph}$ |
| 295 | Same as above | $-\text{C}(=\text{O})-\text{C}(=\text{O})-\text{Ph}$ |

EXAMPLE 2Compounds 296-519

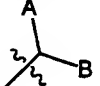
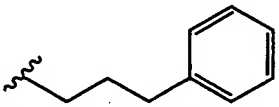
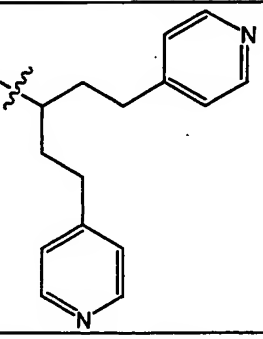
Compounds 296-519 are synthesized via the
 5 method set forth in Scheme 2, above.

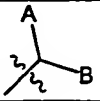
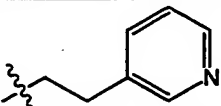
Compounds 296-407 have the formula:




, with the individual variables defined in the table below.

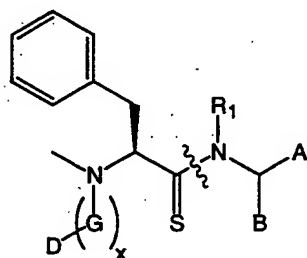
| Cmpd # | A | R ¹ | -(G) _x -D |
|--------|---------------|---------------------------------|----------------------------------|
| 296 | | H | -CH ₃ |
| 297 | Same as above | H | -CH ₂ CH ₃ |
| 298 | Same as above | H | -C(=O)-CH ₃ |
| 299 | Same as above | H | -CH ₂ -Ph |
| 300 | Same as above | H | -C(=O)-Ph |
| 301 | Same as above | H | -C(=O)-O-CH ₂ -Ph |
| 302 | Same as above | H | -C(=O)-C(=O)-Ph |
| 303 | Same as above | CH ₃ | -CH ₃ |
| 304 | Same as above | CH ₃ | -CH ₂ CH ₃ |
| 305 | Same as above | CH ₃ | -C(=O)-CH ₃ |
| 306 | Same as above | CH ₃ | -CH ₂ -Ph |
| 307 | Same as above | CH ₃ | -C(=O)-Ph |
| 308 | Same as above | CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 309 | Same as above | CH ₃ | -C(=O)-C(=O)-Ph |
| 310 | Same as above | CH ₂ CH ₃ | -CH ₃ |
| 311 | Same as above | CH ₂ CH ₃ | -CH ₂ CH ₃ |
| 312 | Same as above | CH ₂ CH ₃ | -C(=O)-CH ₃ |
| 313 | Same as above | CH ₂ CH ₃ | -CH ₂ -Ph |
| 314 | Same as above | CH ₂ CH ₃ | -C(=O)-Ph |
| 315 | Same as above | CH ₂ CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 316 | Same as above | CH ₂ CH ₃ | -C(=O)-C(=O)-Ph |
| 317 | Same as above | CH ₂ Ph | -CH ₃ |
| 318 | Same as above | CH ₂ Ph | -CH ₂ CH ₃ |
| 319 | Same as above | CH ₂ Ph | -C(=O)-CH ₃ |
| 320 | Same as above | CH ₂ Ph | -CH ₂ -Ph |
| 321 | Same as above | CH ₂ Ph | -C(=O)-Ph |

| Cmpd # |  | R ¹ | -(G) _x -D |
|--------|-------------------------------------------------------------------------------------|---------------------------------|----------------------------------|
| 322 | Same as above | CH ₂ Ph | -C(=O)-O-CH ₂ -Ph |
| 323 | Same as above | CH ₂ Ph | -C(=O)-C(=O)-Ph |
| 324 |  | H | -CH ₃ |
| 325 | Same as above | H | -CH ₂ CH ₃ |
| 326 | Same as above | H | -C(=O)-CH ₃ |
| 327 | Same as above | H | -CH ₂ -Ph |
| 328 | Same as above | H | -C(=O)-Ph |
| 329 | Same as above | H | -C(=O)-O-CH ₂ -Ph |
| 330 | Same as above | H | -C(=O)-C(=O)-Ph |
| 331 | Same as above | CH ₃ | -CH ₃ |
| 332 | Same as above | CH ₃ | -CH ₂ CH ₃ |
| 333 | Same as above | CH ₃ | -C(=O)-CH ₃ |
| 334 | Same as above | CH ₃ | -CH ₂ -Ph |
| 335 | Same as above | CH ₃ | -C(=O)-Ph |
| 336 | Same as above | CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 337 | Same as above | CH ₃ | -C(=O)-C(=O)-Ph |
| 338 | Same as above | CH ₂ CH ₃ | -CH ₃ |
| 339 | Same as above | CH ₂ CH ₃ | -CH ₂ CH ₃ |
| 340 | Same as above | CH ₂ CH ₃ | -C(=O)-CH ₃ |
| 341 | Same as above | CH ₂ CH ₃ | -CH ₂ -Ph |
| 342 | Same as above | CH ₂ CH ₃ | -C(=O)-Ph |
| 343 | Same as above | CH ₂ CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 344 | Same as above | CH ₂ CH ₃ | -C(=O)-C(=O)-Ph |
| 345 | Same as above | CH ₂ Ph | -CH ₃ |
| 346 | Same as above | CH ₂ Ph | -CH ₂ CH ₃ |
| 347 | Same as above | CH ₂ Ph | -C(=O)-CH ₃ |
| 348 | Same as above | CH ₂ Ph | -CH ₂ -Ph |
| 349 | Same as above | CH ₂ Ph | -C(=O)-Ph |
| 350 | Same as above | CH ₂ Ph | -C(=O)-O-CH ₂ -Ph |
| 351 | Same as above | CH ₂ Ph | -C(=O)-C(=O)-Ph |
| 352 |  | H | -CH ₃ |
| 353 | Same as above | H | -CH ₂ CH ₃ |


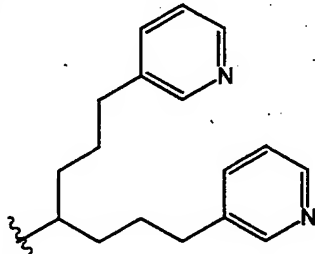
| Cmpd # |  | R ¹ | -(G) _x -D |
|--------|-------------------------------------------------------------------------------------|---------------------------------|----------------------------------|
| 354 | Same as above | H | -C(=O)-CH ₃ |
| 355 | Same as above | H | -CH ₂ -Ph |
| 356 | Same as above | H | -C(=O)-Ph |
| 357 | Same as above | H | -C(=O)-O-CH ₂ -Ph |
| 358 | Same as above | H | -C(=O)-C(=O)-Ph |
| 359 | Same as above | CH ₃ | -CH ₃ |
| 360 | Same as above | CH ₃ | -CH ₂ CH ₃ |
| 361 | Same as above | CH ₃ | -C(=O)-CH ₃ |
| 362 | Same as above | CH ₃ | -CH ₂ -Ph |
| 363 | Same as above | CH ₃ | -C(=O)-Ph |
| 364 | Same as above | CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 365 | Same as above | CH ₃ | -C(=O)-C(=O)-Ph |
| 366 | Same as above | CH ₂ CH ₃ | -CH ₃ |
| 367 | Same as above | CH ₂ CH ₃ | -CH ₂ CH ₃ |
| 368 | Same as above | CH ₂ CH ₃ | -C(=O)-CH ₃ |
| 369 | Same as above | CH ₂ CH ₃ | -CH ₂ -Ph |
| 370 | Same as above | CH ₂ CH ₃ | -C(=O)-Ph |
| 371 | Same as above | CH ₂ CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 372 | Same as above | CH ₂ CH ₃ | -C(=O)-C(=O)-Ph |
| 373 | Same as above | CH ₂ Ph | -CH ₃ |
| 374 | Same as above | CH ₂ Ph | -CH ₂ CH ₃ |
| 375 | Same as above | CH ₂ Ph | -C(=O)-CH ₃ |
| 376 | Same as above | CH ₂ Ph | -CH ₂ -Ph |
| 377 | Same as above | CH ₂ Ph | -C(=O)-Ph |
| 378 | Same as above | CH ₂ Ph | -C(=O)-O-CH ₂ -Ph |
| 379 | Same as above | CH ₂ Ph | -C(=O)-C(=O)-Ph |
| 380 |  | H | -CH ₃ |
| 381 | Same as above | H | -CH ₂ CH ₃ |
| 382 | Same as above | H | -C(=O)-CH ₃ |
| 383 | Same as above | H | -CH ₂ -Ph |
| 384 | Same as above | H | -C(=O)-Ph |
| 385 | Same as above | H | -C(=O)-O-CH ₂ -Ph |
| 386 | Same as above | H | -C(=O)-C(=O)-Ph |
| 387 | Same as above | CH ₃ | -CH ₃ |
| 388 | Same as above | CH ₃ | -CH ₂ CH ₃ |
| 389 | Same as above | CH ₃ | -C(=O)-CH ₃ |
| 390 | Same as above | CH ₃ | -CH ₂ -Ph |
| 391 | Same as above | CH ₃ | -C(=O)-Ph |
| 392 | Same as above | CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 393 | Same as above | CH ₃ | -C(=O)-C(=O)-Ph |


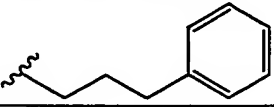
| Cmpd # |  | R ¹ | -(G) _x -D |
|--------|-----------------------------------------------------------------------------------|---------------------------------|----------------------------------|
| 394 | Same as above | CH ₂ CH ₃ | -CH ₃ |
| 395 | Same as above | CH ₂ CH ₃ | -CH ₂ CH ₃ |
| 396 | Same as above | CH ₂ CH ₃ | -C(=O)-CH ₃ |
| 397 | Same as above | CH ₂ CH ₃ | -CH ₂ -Ph |
| 398 | Same as above | CH ₂ CH ₃ | -C(=O)-Ph |
| 399 | Same as above | CH ₂ CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 400 | Same as above | CH ₂ CH ₃ | -C(=O)-C(=O)-Ph |
| 401 | Same as above | CH ₂ Ph | -CH ₃ |
| 402 | Same as above | CH ₂ Ph | -CH ₂ CH ₃ |
| 403 | Same as above | CH ₂ Ph | -C(=O)-CH ₃ |
| 404 | Same as above | CH ₂ Ph | -CH ₂ -Ph |
| 405 | Same as above | CH ₂ Ph | -C(=O)-Ph |
| 406 | Same as above | CH ₂ Ph | -C(=O)-O-CH ₂ -Ph |
| 407 | Same as above | CH ₂ Ph | -C(=O)-C(=O)-Ph |

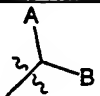
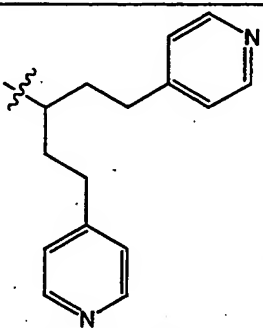
Compounds 408-519 have the formula:

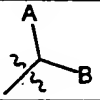
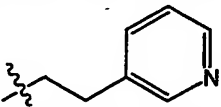


, with the individual variables defined in the table below.

| Cmpd # |  | R ¹ | -(G) _x -D |
|--------|-------------------------------------------------------------------------------------|----------------|----------------------------------|
| 408 |  | H | -CH ₃ |
| 409 | Same as above | H | -CH ₂ CH ₃ |
| 410 | Same as above | H | -C(=O)-CH ₃ |
| 411 | Same as above | H | -CH ₂ -Ph |
| 412 | Same as above | H | -C(=O)-Ph |
| 413 | Same as above | H | -C(=O)-O-CH ₂ -Ph |

| Cmpd # |  | R ¹ | -(G) _x -D |
|--------|-------------------------------------------------------------------------------------|---------------------------------|----------------------------------|
| 414 | Same as above | H | -C(=O)-C(=O)-Ph |
| 415 | Same as above | CH ₃ | -CH ₃ |
| 416 | Same as above | CH ₃ | -CH ₂ CH ₃ |
| 417 | Same as above | CH ₃ | -C(=O)-CH ₃ |
| 418 | Same as above | CH ₃ | -CH ₂ -Ph |
| 419 | Same as above | CH ₃ | -C(=O)-Ph |
| 420 | Same as above | CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 421 | Same as above | CH ₃ | -C(=O)-C(=O)-Ph |
| 422 | Same as above | CH ₂ CH ₃ | -CH ₃ |
| 423 | Same as above | CH ₂ CH ₃ | -CH ₂ CH ₃ |
| 424 | Same as above | CH ₂ CH ₃ | -C(=O)-CH ₃ |
| 425 | Same as above | CH ₂ CH ₃ | -CH ₂ -Ph |
| 426 | Same as above | CH ₂ CH ₃ | -C(=O)-Ph |
| 427 | Same as above | CH ₂ CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 428 | Same as above | CH ₂ CH ₃ | -C(=O)-C(=O)-Ph |
| 429 | Same as above | CH ₂ Ph | -CH ₃ |
| 430 | Same as above | CH ₂ Ph | -CH ₂ CH ₃ |
| 431 | Same as above | CH ₂ Ph | -C(=O)-CH ₃ |
| 432 | Same as above | CH ₂ Ph | -CH ₂ -Ph |
| 433 | Same as above | CH ₂ Ph | -C(=O)-Ph |
| 434 | Same as above | CH ₂ Ph | -C(=O)-O-CH ₂ -Ph |
| 435 | Same as above | CH ₂ Ph | -C(=O)-C(=O)-Ph |
| 436 |  | H | -CH ₃ |
| 437 | Same as above | H | -CH ₂ CH ₃ |
| 438 | Same as above | H | -C(=O)-CH ₃ |
| 439 | Same as above | H | -CH ₂ -Ph |
| 440 | Same as above | H | -C(=O)-Ph |
| 441 | Same as above | H | -C(=O)-O-CH ₂ -Ph |
| 442 | Same as above | H | -C(=O)-C(=O)-Ph |
| 443 | Same as above | CH ₃ | -CH ₃ |
| 444 | Same as above | CH ₃ | -CH ₂ CH ₃ |
| 445 | Same as above | CH ₃ | -C(=O)-CH ₃ |
| 446 | Same as above | CH ₃ | -CH ₂ -Ph |
| 447 | Same as above | CH ₃ | -C(=O)-Ph |
| 448 | Same as above | CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 449 | Same as above | CH ₃ | -C(=O)-C(=O)-Ph |
| 450 | Same as above | CH ₂ CH ₃ | -CH ₃ |
| 451 | Same as above | CH ₂ CH ₃ | -CH ₂ CH ₃ |
| 452 | Same as above | CH ₂ CH ₃ | -C(=O)-CH ₃ |
| 453 | Same as above | CH ₂ CH ₃ | -CH ₂ -Ph |

| Cmpd # |  | R ¹ | -(G) _x -D |
|--------|------------------------------------------------------------------------------------|---------------------------------|----------------------------------|
| 454 | Same as above | CH ₂ CH ₃ | -C(=O)-Ph |
| 455 | Same as above | CH ₂ CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 456 | Same as above | CH ₂ CH ₃ | -C(=O)-C(=O)-Ph |
| 457 | Same as above | CH ₂ Ph | -CH ₃ |
| 458 | Same as above | CH ₂ Ph | -CH ₂ CH ₃ |
| 459 | Same as above | CH ₂ Ph | -C(=O)-CH ₃ |
| 460 | Same as above | CH ₂ Ph | -CH ₂ -Ph |
| 461 | Same as above | CH ₂ Ph | -C(=O)-Ph |
| 462 | Same as above | CH ₂ Ph | -C(=O)-O-CH ₂ -Ph |
| 463 | Same as above | CH ₂ Ph | -C(=O)-C(=O)-Ph |
| 464 |  | H | -CH ₃ |
| 465 | Same as above | H | -CH ₂ CH ₃ |
| 466 | Same as above | H | -C(=O)-CH ₃ |
| 467 | Same as above | H | -CH ₂ -Ph |
| 468 | Same as above | H | -C(=O)-Ph |
| 469 | Same as above | H | -C(=O)-O-CH ₂ -Ph |
| 470 | Same as above | H | -C(=O)-C(=O)-Ph |
| 471 | Same as above | CH ₃ | -CH ₃ |
| 472 | Same as above | CH ₃ | -CH ₂ CH ₃ |
| 473 | Same as above | CH ₃ | -C(=O)-CH ₃ |
| 474 | Same as above | CH ₃ | -CH ₂ -Ph |
| 475 | Same as above | CH ₃ | -C(=O)-Ph |
| 476 | Same as above | CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 477 | Same as above | CH ₃ | -C(=O)-C(=O)-Ph |
| 478 | Same as above | CH ₂ CH ₃ | -CH ₃ |
| 479 | Same as above | CH ₂ CH ₃ | -CH ₂ CH ₃ |
| 480 | Same as above | CH ₂ CH ₃ | -C(=O)-CH ₃ |
| 481 | Same as above | CH ₂ CH ₃ | -CH ₂ -Ph |
| 482 | Same as above | CH ₂ CH ₃ | -C(=O)-Ph |
| 483 | Same as above | CH ₂ CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 484 | Same as above | CH ₂ CH ₃ | -C(=O)-C(=O)-Ph |
| 485 | Same as above | CH ₂ Ph | -CH ₃ |
| 486 | Same as above | CH ₂ Ph | -CH ₂ CH ₃ |
| 487 | Same as above | CH ₂ Ph | -C(=O)-CH ₃ |

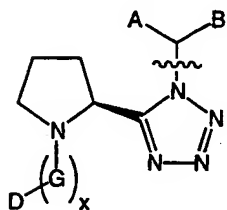
| Cmpd # |  | R ¹ | -(G) _x -D |
|--------|-----------------------------------------------------------------------------------|---------------------------------|----------------------------------|
| 488 | Same as above | CH ₂ Ph | -CH ₂ -Ph |
| 489 | Same as above | CH ₂ Ph | -C(=O)-Ph |
| 490 | Same as above | CH ₂ Ph | -C(=O)-O-CH ₂ -Ph |
| 491 | Same as above | CH ₂ Ph | -C(=O)-C(=O)-Ph |
| 492 |  | H | -CH ₃ |
| 493 | Same as above | H | -CH ₂ CH ₃ |
| 494 | Same as above | H | -C(=O)-CH ₃ |
| 495 | Same as above | H | -CH ₂ -Ph |
| 496 | Same as above | H | -C(=O)-Ph |
| 497 | Same as above | H | -C(=O)-O-CH ₂ -Ph |
| 498 | Same as above | H | -C(=O)-C(=O)-Ph |
| 499 | Same as above | CH ₃ | -CH ₃ |
| 500 | Same as above | CH ₃ | -CH ₂ CH ₃ |
| 501 | Same as above | CH ₃ | -C(=O)-CH ₃ |
| 502 | Same as above | CH ₃ | -CH ₂ -Ph |
| 503 | Same as above | CH ₃ | -C(=O)-Ph |
| 504 | Same as above | CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 505 | Same as above | CH ₃ | -C(=O)-C(=O)-Ph |
| 506 | Same as above | CH ₂ CH ₃ | -CH ₃ |
| 507 | Same as above | CH ₂ CH ₃ | -CH ₂ CH ₃ |
| 508 | Same as above | CH ₂ CH ₃ | -C(=O)-CH ₃ |
| 509 | Same as above | CH ₂ CH ₃ | -CH ₂ -Ph |
| 510 | Same as above | CH ₂ CH ₃ | -C(=O)-Ph |
| 511 | Same as above | CH ₂ CH ₃ | -C(=O)-O-CH ₂ -Ph |
| 512 | Same as above | CH ₂ CH ₃ | -C(=O)-C(=O)-Ph |
| 513 | Same as above | CH ₂ Ph | -CH ₃ |
| 514 | Same as above | CH ₂ Ph | -CH ₂ CH ₃ |
| 515 | Same as above | CH ₂ Ph | -C(=O)-CH ₃ |
| 516 | Same as above | CH ₂ Ph | -CH ₂ -Ph |
| 517 | Same as above | CH ₂ Ph | -C(=O)-Ph |
| 518 | Same as above | CH ₂ Ph | -C(=O)-O-CH ₂ -Ph |
| 519 | Same as above | CH ₂ Ph | -C(=O)-C(=O)-Ph |

EXAMPLE 3


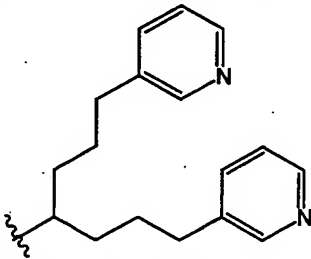
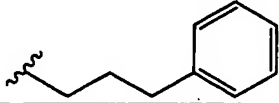
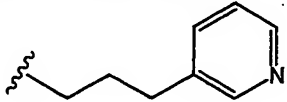
Compounds 520-561

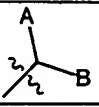
Compounds 520-561 are synthesized via the method set forth in Scheme 3, above.

5 Compounds 520-540 have the formula:

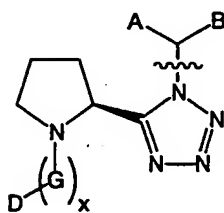


$D^{(1)}_x$, with the individual variables defined in the table below.

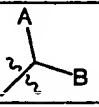
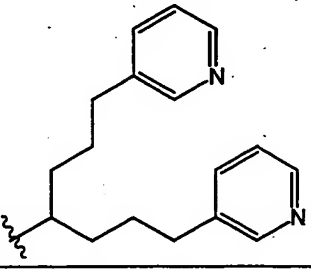
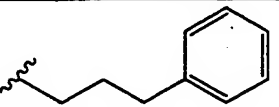
| Cmpd. # |  | - (G) _x -D |
|---------|-------------------------------------------------------------------------------------|----------------------------------|
| 520 |  | -CH ₃ |
| 521 | Same as above | -CH ₂ CH ₃ |
| 522 | Same as above | -C(=O)-CH ₃ |
| 523 | Same as above | -CH ₂ -Ph |
| 524 | Same as above | -C(=O)-Ph |
| 525 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 526 | Same as above | -C(=O)-C(=O)-Ph |
| 527 |  | -CH ₃ |
| 528 | Same as above | -CH ₂ CH ₃ |
| 529 | Same as above | -C(=O)-CH ₃ |
| 530 | Same as above | -CH ₂ -Ph |
| 531 | Same as above | -C(=O)-Ph |
| 532 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 533 | Same as above | -C(=O)-C(=O)-Ph |
| 534 |  | -CH ₃ |


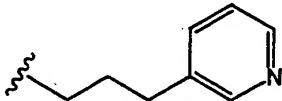
| Cmpd # |  | $-(G)_x-D$ |
|--------|-----------------------------------------------------------------------------------|--------------------|
| 535 | Same as above | $-CH_2CH_3$ |
| 536 | Same as above | $-C(=O)-CH_3$ |
| 537 | Same as above | $-CH_2-Ph$ |
| 538 | Same as above | $-C(=O)-Ph$ |
| 539 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 540 | Same as above | $-C(=O)-C(=O)-Ph$ |

Compounds 541-561 have the formula:



, with the individual variables defined in the table below.

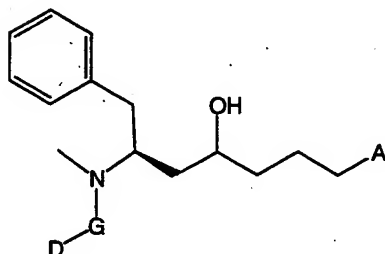
| Cmpd # |  | $-(G)_x-D$ |
|--------|-------------------------------------------------------------------------------------|--------------------|
| 541 |  | $-CH_3$ |
| 542 | Same as above | $-CH_2CH_3$ |
| 543 | Same as above | $-C(=O)-CH_3$ |
| 544 | Same as above | $-CH_2-Ph$ |
| 545 | Same as above | $-C(=O)-Ph$ |
| 546 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 547 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 548 |  | $-CH_3$ |
| 549 | Same as above | $-CH_2CH_3$ |
| 550 | Same as above | $-C(=O)-CH_3$ |
| 551 | Same as above | $-CH_2-Ph$ |
| 552 | Same as above | $-C(=O)-Ph$ |
| 553 | Same as above | $-C(=O)-O-CH_2-Ph$ |

| Cmpd # | A  | $-(G)_x-D$ |
|--------|----------------------------------------------------------------------------------------|--------------------|
| 554 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 555 |  | $-CH_3$ |
| 556 | Same as above | $-CH_2CH_3$ |
| 557 | Same as above | $-C(=O)-CH_3$ |
| 558 | Same as above | $-CH_2-Ph$ |
| 559 | Same as above | $-C(=O)-Ph$ |
| 560 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 561 | Same as above | $-C(=O)-C(=O)-Ph$ |

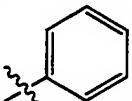
EXAMPLE 4Compounds 562-771

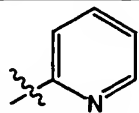
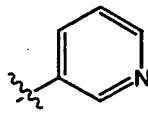
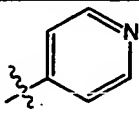
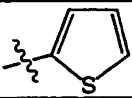
Compounds 562-771 are synthesized via the method set forth in Scheme 4 or Scheme 6, above.

Compounds 562-596 have the formula:



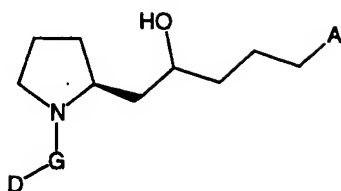
, with the individual variables defined in the table below.

| Cmpd # | A  | $-(G)_x-D$ |
|--------|------------------------------------------------------------------------------------------|--------------------|
| 562 | Same as above | $-CH_3$ |
| 563 | Same as above | $-CH_2CH_3$ |
| 564 | Same as above | $-C(=O)-CH_3$ |
| 565 | Same as above | $-CH_2-Ph$ |
| 566 | Same as above | $-C(=O)-Ph$ |
| 567 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 568 | Same as above | $-C(=O)-C(=O)-Ph$ |

| Cmpd # | A | $-(G)_x-D$ |
|--------|-------------------------------------------------------------------------------------|--------------------|
| 569 |  | $-CH_3$ |
| 570 | Same as above | $-CH_2CH_3$ |
| 571 | Same as above | $-C(=O)-CH_3$ |
| 572 | Same as above | $-CH_2-Ph$ |
| 573 | Same as above | $-C(=O)-Ph$ |
| 574 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 575 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 576 |  | $-CH_3$ |
| 577 | Same as above | $-CH_2CH_3$ |
| 578 | Same as above | $-C(=O)-CH_3$ |
| 579 | Same as above | $-CH_2-Ph$ |
| 580 | Same as above | $-C(=O)-Ph$ |
| 581 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 582 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 583 |  | $-CH_3$ |
| 584 | Same as above | $-CH_2CH_3$ |
| 585 | Same as above | $-C(=O)-CH_3$ |
| 586 | Same as above | $-CH_2-Ph$ |
| 587 | Same as above | $-C(=O)-Ph$ |
| 588 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 589 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 590 |  | $-CH_3$ |
| 591 | Same as above | $-CH_2CH_3$ |
| 592 | Same as above | $-C(=O)-CH_3$ |
| 593 | Same as above | $-CH_2-Ph$ |
| 594 | Same as above | $-C(=O)-Ph$ |
| 595 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 596 | Same as above | $-C(=O)-C(=O)-Ph$ |
| | | |

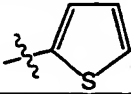
Compounds 597-631 have the formula:

-51-

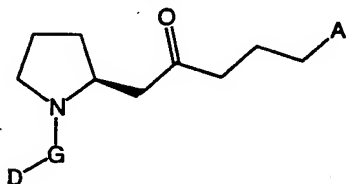


, with the individual variables defined in the table below.

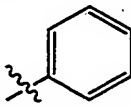
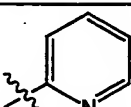
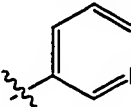
| Cmpd # | A | - (G) _x -D |
|--------|---------------|----------------------------------|
| 597 | | -CH ₃ |
| 598 | Same as above | -CH ₂ CH ₃ |
| 599 | Same as above | -C(=O)-CH ₃ |
| 600 | Same as above | -CH ₂ -Ph |
| 601 | Same as above | -C(=O)-Ph |
| 602 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 603 | Same as above | -C(=O)-C(=O)-Ph |
| 604 | | -CH ₃ |
| 605 | Same as above | -CH ₂ CH ₃ |
| 606 | Same as above | -C(=O)-CH ₃ |
| 607 | Same as above | -CH ₂ -Ph |
| 608 | Same as above | -C(=O)-Ph |
| 609 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 610 | Same as above | -C(=O)-C(=O)-Ph |
| 611 | | -CH ₃ |
| 612 | Same as above | -CH ₂ CH ₃ |
| 613 | Same as above | -C(=O)-CH ₃ |
| 614 | Same as above | -CH ₂ -Ph |
| 615 | Same as above | -C(=O)-Ph |
| 616 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 617 | Same as above | -C(=O)-C(=O)-Ph |
| 618 | | -CH ₃ |
| 619 | Same as above | -CH ₂ CH ₃ |
| 620 | Same as above | -C(=O)-CH ₃ |
| 621 | Same as above | -CH ₂ -Ph |
| 622 | Same as above | -C(=O)-Ph |

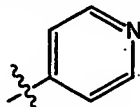
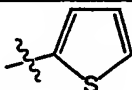
| Cmpd # | A | $-(G)_x-D$ |
|--------|-----------------------------------------------------------------------------------|--------------------|
| 623 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 624 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 625 |  | $-CH_3$ |
| 626 | Same as above | $-CH_2CH_3$ |
| 627 | Same as above | $-C(=O)-CH_3$ |
| 628 | Same as above | $-CH_2-Ph$ |
| 629 | Same as above | $-C(=O)-Ph$ |
| 630 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 631 | Same as above | $-C(=O)-C(=O)-Ph$ |

Compounds 632-666 have the formula:

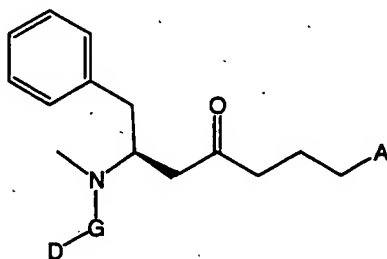


, with the individual variables defined in the table below.

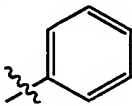
| Cmpd # | A | $-(G)_x-D$ |
|--------|-------------------------------------------------------------------------------------|--------------------|
| 632 |  | $-CH_3$ |
| 633 | Same as above | $-CH_2CH_3$ |
| 634 | Same as above | $-C(=O)-CH_3$ |
| 635 | Same as above | $-CH_2-Ph$ |
| 636 | Same as above | $-C(=O)-Ph$ |
| 637 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 638 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 639 |  | $-CH_3$ |
| 640 | Same as above | $-CH_2CH_3$ |
| 641 | Same as above | $-C(=O)-CH_3$ |
| 642 | Same as above | $-CH_2-Ph$ |
| 643 | Same as above | $-C(=O)-Ph$ |
| 644 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 645 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 646 |  | $-CH_3$ |

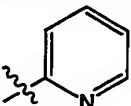
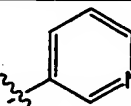
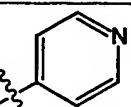
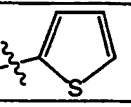
| Cmpd # | A | $-(G)_x-D$ |
|--------|-----------------------------------------------------------------------------------|--------------------|
| 647 | Same as above | $-CH_2CH_3$ |
| 648 | Same as above | $-C(=O)-CH_3$ |
| 649 | Same as above | $-CH_2-Ph$ |
| 650 | Same as above | $-C(=O)-Ph$ |
| 651 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 652 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 653 |  | $-CH_3$ |
| 654 | Same as above | $-CH_2CH_3$ |
| 655 | Same as above | $-C(=O)-CH_3$ |
| 656 | Same as above | $-CH_2-Ph$ |
| 657 | Same as above | $-C(=O)-Ph$ |
| 658 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 659 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 660 |  | $-CH_3$ |
| 661 | Same as above | $-CH_2CH_3$ |
| 662 | Same as above | $-C(=O)-CH_3$ |
| 663 | Same as above | $-CH_2-Ph$ |
| 664 | Same as above | $-C(=O)-Ph$ |
| 665 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 666 | Same as above | $-C(=O)-C(=O)-Ph$ |

Compounds 667-701 have the formula:

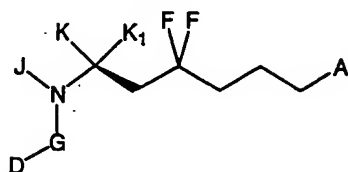


, with the individual variables defined in the table below.

| Cmpd # | A | $-(G)_x-D$ |
|--------|-------------------------------------------------------------------------------------|---------------|
| 667 |  | $-CH_3$ |
| 668 | Same as above | $-CH_2CH_3$ |
| 669 | Same as above | $-C(=O)-CH_3$ |
| 670 | Same as above | $-CH_2-Ph$ |

| Cmpd # | A | - (G) _x -D |
|--------|-------------------------------------------------------------------------------------|----------------------------------|
| 671 | Same as above | -C(=O)-Ph |
| 672 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 673 | Same as above | -C(=O)-C(=O)-Ph |
| 674 |  | -CH ₃ |
| 675 | Same as above | -CH ₂ CH ₃ |
| 676 | Same as above | -C(=O)-CH ₃ |
| 677 | Same as above | -CH ₂ -Ph |
| 678 | Same as above | -C(=O)-Ph |
| 679 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 680 | Same as above | -C(=O)-C(=O)-Ph |
| 681 |  | -CH ₃ |
| 682 | Same as above | -CH ₂ CH ₃ |
| 683 | Same as above | -C(=O)-CH ₃ |
| 684 | Same as above | -CH ₂ -Ph |
| 685 | Same as above | -C(=O)-Ph |
| 686 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 687 | Same as above | -C(=O)-C(=O)-Ph |
| 688 |  | -CH ₃ |
| 689 | Same as above | -CH ₂ CH ₃ |
| 690 | Same as above | -C(=O)-CH ₃ |
| 691 | Same as above | -CH ₂ -Ph |
| 692 | Same as above | -C(=O)-Ph |
| 693 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 694 | Same as above | -C(=O)-C(=O)-Ph |
| 695 |  | -CH ₃ |
| 696 | Same as above | -CH ₂ CH ₃ |
| 697 | Same as above | -C(=O)-CH ₃ |
| 698 | Same as above | -CH ₂ -Ph |
| 699 | Same as above | -C(=O)-Ph |
| 700 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 701 | Same as above | -C(=O)-C(=O)-Ph |

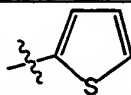
Compounds 702-736 have the formula:



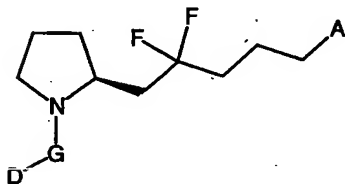
, with the individual variables defined in the table below.

5

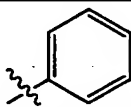
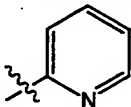
| Cmpd # | A | - (G) _x -D |
|--------|---------------|----------------------------------|
| 702 | | -CH ₃ |
| 703 | Same as above | -CH ₂ CH ₃ |
| 704 | Same as above | -C(=O)-CH ₃ |
| 705 | Same as above | -CH ₂ -Ph |
| 706 | Same as above | -C(=O)-Ph |
| 707 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 708 | Same as above | -C(=O)-C(=O)-Ph |
| 709 | | -CH ₃ |
| 710 | Same as above | -CH ₂ CH ₃ |
| 711 | Same as above | -C(=O)-CH ₃ |
| 712 | Same as above | -CH ₂ -Ph |
| 713 | Same as above | -C(=O)-Ph |
| 714 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 715 | Same as above | -C(=O)-C(=O)-Ph |
| 716 | | -CH ₃ |
| 717 | Same as above | -CH ₂ CH ₃ |
| 718 | Same as above | -C(=O)-CH ₃ |
| 719 | Same as above | -CH ₂ -Ph |
| 720 | Same as above | -C(=O)-Ph |
| 721 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 722 | Same as above | -C(=O)-C(=O)-Ph |
| 723 | | -CH ₃ |
| 724 | Same as above | -CH ₂ CH ₃ |

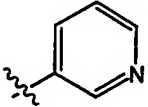
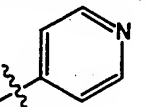
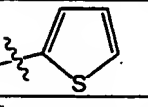
| Cmpd # | A | $-(G)_x-D$ |
|--------|-----------------------------------------------------------------------------------|--------------------|
| 725 | Same as above | $-C(=O)-CH_3$ |
| 726 | Same as above | $-CH_2-Ph$ |
| 727 | Same as above | $-C(=O)-Ph$ |
| 728 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 729 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 730 |  | $-CH_3$ |
| 731 | Same as above | $-CH_2CH_3$ |
| 732 | Same as above | $-C(=O)-CH_3$ |
| 733 | Same as above | $-CH_2-Ph$ |
| 734 | Same as above | $-C(=O)-Ph$ |
| 735 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 736 | Same as above | $-C(=O)-C(=O)-Ph$ |

Compounds 737-771 have the formula:



, with the individual variables defined in the table below.

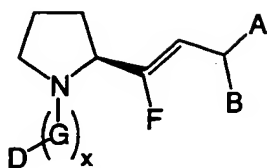
| Cmpd # | A | $-(G)_x-D$ |
|--------|-------------------------------------------------------------------------------------|--------------------|
| 737 |  | $-CH_3$ |
| 738 | Same as above | $-CH_2CH_3$ |
| 739 | Same as above | $-C(=O)-CH_3$ |
| 740 | Same as above | $-CH_2-Ph$ |
| 741 | Same as above | $-C(=O)-Ph$ |
| 742 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 743 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 744 |  | $-CH_3$ |
| 745 | Same as above | $-CH_2CH_3$ |
| 746 | Same as above | $-C(=O)-CH_3$ |
| 747 | Same as above | $-CH_2-Ph$ |
| 748 | Same as above | $-C(=O)-Ph$ |
| 749 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 750 | Same as above | $-C(=O)-C(=O)-Ph$ |

| Cmpd # | A | - (G) _x -D |
|--------|------------------------------------------------------------------------------------|----------------------------------|
| 751 |  | -CH ₃ |
| 752 | Same as above | -CH ₂ CH ₃ |
| 753 | Same as above | -C(=O)-CH ₃ |
| 754 | Same as above | -CH ₂ -Ph |
| 755 | Same as above | -C(=O)-Ph |
| 756 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 757 | Same as above | -C(=O)-C(=O)-Ph |
| 758 |  | -CH ₃ |
| 759 | Same as above | -CH ₂ CH ₃ |
| 760 | Same as above | -C(=O)-CH ₃ |
| 761 | Same as above | -CH ₂ -Ph |
| 762 | Same as above | -C(=O)-Ph |
| 763 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 764 | Same as above | -C(=O)-C(=O)-Ph |
| 765 |  | -CH ₃ |
| 766 | Same as above | -CH ₂ CH ₃ |
| 767 | Same as above | -C(=O)-CH ₃ |
| 768 | Same as above | -CH ₂ -Ph |
| 769 | Same as above | -C(=O)-Ph |
| 770 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 771 | Same as above | -C(=O)-C(=O)-Ph |


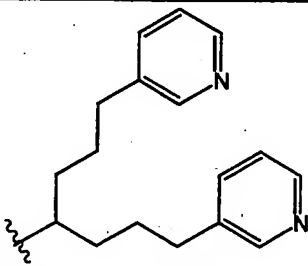
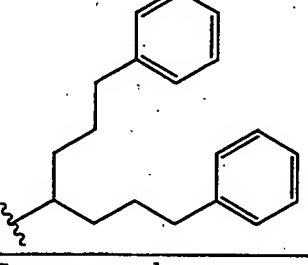
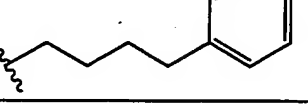
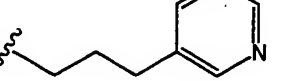
EXAMPLE 5Compounds 772-967


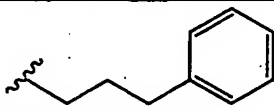
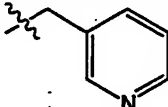
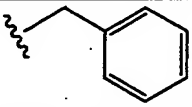
5 Compounds 772- are synthesized via the method set forth in Scheme 5, above.

Compounds 772-820 have the formula:

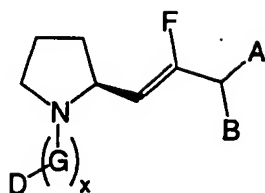


, with the individual variables defined in the table below

| Cmpd # |  | $-(G)_x-D$ |
|--------|-------------------------------------------------------------------------------------|--------------------|
| 772 |  | $-CH_3$ |
| 773 | Same as above | $-CH_2CH_3$ |
| 774 | Same as above | $-C(=O)-CH_3$ |
| 775 | Same as above | $-CH_2-Ph$ |
| 776 | Same as above | $-C(=O)-Ph$ |
| 777 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 778 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 779 |  | $-CH_3$ |
| 780 | Same as above | $-CH_2CH_3$ |
| 781 | Same as above | $-C(=O)-CH_3$ |
| 782 | Same as above | $-CH_2-Ph$ |
| 783 | Same as above | $-C(=O)-Ph$ |
| 784 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 785 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 786 |  | $-CH_3$ |
| 787 | Same as above | $-CH_2CH_3$ |
| 788 | Same as above | $-C(=O)-CH_3$ |
| 789 | Same as above | $-CH_2-Ph$ |
| 790 | Same as above | $-C(=O)-Ph$ |
| 791 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 792 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 793 |  | $-CH_3$ |


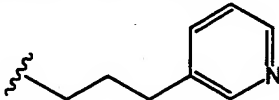
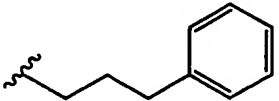
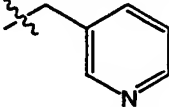
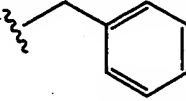
| Cmpd # |  | - (G) _x -D |
|--------|-------------------------------------------------------------------------------------|----------------------------------|
| 794 | Same as above | -CH ₂ CH ₃ |
| 795 | Same as above | -C(=O)-CH ₃ |
| 796 | Same as above | -CH ₂ -Ph |
| 797 | Same as above | -C(=O)-Ph |
| 798 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 799 | Same as above | -C(=O)-C(=O)-Ph |
| 800 |  | -CH ₃ |
| 801 | Same as above | -CH ₂ CH ₃ |
| 802 | Same as above | -C(=O)-CH ₃ |
| 803 | Same as above | -CH ₂ -Ph |
| 804 | Same as above | -C(=O)-Ph |
| 805 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 806 | Same as above | -C(=O)-C(=O)-Ph |
| 807 |  | -CH ₃ |
| 808 | Same as above | -CH ₂ CH ₃ |
| 809 | Same as above | -C(=O)-CH ₃ |
| 810 | Same as above | -CH ₂ -Ph |
| 811 | Same as above | -C(=O)-Ph |
| 812 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 813 | Same as above | -C(=O)-C(=O)-Ph |
| 814 |  | -CH ₃ |
| 815 | Same as above | -CH ₂ CH ₃ |
| 816 | Same as above | -C(=O)-CH ₃ |
| 817 | Same as above | -CH ₂ -Ph |
| 818 | Same as above | -C(=O)-Ph |
| 819 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 820 | Same as above | -C(=O)-C(=O)-Ph |

Compounds 821-869 have the formula:

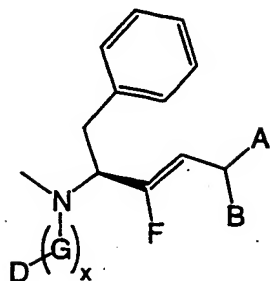


, with the individual variables defined in the table below

| Cmpd # | | $-(G)_x-D$ |
|--------|---------------|--------------------|
| 821 | | $-CH_3$ |
| 822 | Same as above | $-CH_2CH_3$ |
| 823 | Same as above | $-C(=O)-CH_3$ |
| 824 | Same as above | $-CH_2-Ph$ |
| 825 | Same as above | $-C(=O)-Ph$ |
| 826 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 827 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 828 | | $-CH_3$ |
| 829 | Same as above | $-CH_2CH_3$ |
| 830 | Same as above | $-C(=O)-CH_3$ |
| 831 | Same as above | $-CH_2-Ph$ |
| 832 | Same as above | $-C(=O)-Ph$ |
| 833 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 834 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 835 | | $-CH_3$ |
| 836 | Same as above | $-CH_2CH_3$ |
| 837 | Same as above | $-C(=O)-CH_3$ |


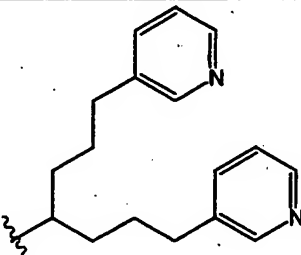
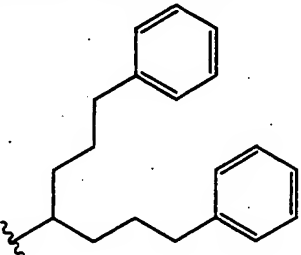
| Cmpd # |  | - (G) _x -D |
|--------|-------------------------------------------------------------------------------------|----------------------------------|
| 838 | Same as above | -CH ₂ -Ph |
| 839 | Same as above | -C(=O)-Ph |
| 840 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 841 | Same as above | -C(=O)-C(=O)-Ph |
| 842 |  | -CH ₃ |
| 843 | Same as above | -CH ₂ CH ₃ |
| 844 | Same as above | -C(=O)-CH ₃ |
| 845 | Same as above | -CH ₂ -Ph |
| 846 | Same as above | -C(=O)-Ph |
| 847 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 848 | Same as above | -C(=O)-C(=O)-Ph |
| 849 |  | -CH ₃ |
| 850 | Same as above | -CH ₂ CH ₃ |
| 851 | Same as above | -C(=O)-CH ₃ |
| 852 | Same as above | -CH ₂ -Ph |
| 853 | Same as above | -C(=O)-Ph |
| 854 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 855 | Same as above | -C(=O)-C(=O)-Ph |
| 856 |  | -CH ₃ |
| 857 | Same as above | -CH ₂ CH ₃ |
| 858 | Same as above | -C(=O)-CH ₃ |
| 859 | Same as above | -CH ₂ -Ph |
| 860 | Same as above | -C(=O)-Ph |
| 861 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 862 | Same as above | -C(=O)-C(=O)-Ph |
| 863 |  | -CH ₃ |
| 864 | Same as above | -CH ₂ CH ₃ |
| 865 | Same as above | -C(=O)-CH ₃ |
| 866 | Same as above | -CH ₂ -Ph |
| 867 | Same as above | -C(=O)-Ph |
| 868 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 869 | Same as above | -C(=O)-C(=O)-Ph |


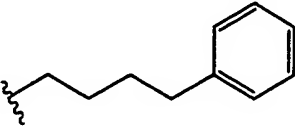
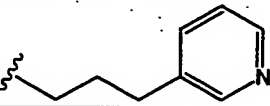
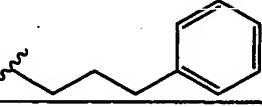
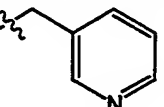
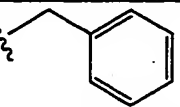
Compounds 870-918 have the formula:

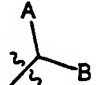


, with the individual variables defined in the table below

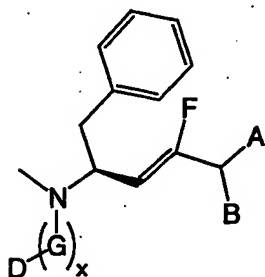
5

| Cmpd # |  | - (G) _x -D |
|--------|-------------------------------------------------------------------------------------|----------------------------------|
| 870 |  | -CH ₃ |
| 871 | Same as above | -CH ₂ CH ₃ |
| 872 | Same as above | -C(=O)-CH ₃ |
| 873 | Same as above | -CH ₂ -Ph |
| 874 | Same as above | -C(=O)-Ph |
| 875 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 876 | Same as above | -C(=O)-C(=O)-Ph |
| 877 |  | -CH ₃ |
| 878 | Same as above | -CH ₂ CH ₃ |
| 879 | Same as above | -C(=O)-CH ₃ |
| 880 | Same as above | -CH ₂ -Ph |
| 881 | Same as above | -C(=O)-Ph |
| 882 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 883 | Same as above | -C(=O)-C(=O)-Ph |

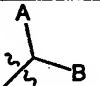
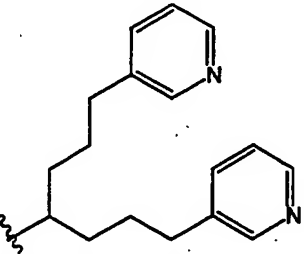
| Compd # |  | $-(G)_x-D$ |
|---------|-------------------------------------------------------------------------------------|--------------------|
| 884 |  | $-CH_3$ |
| 885 | Same as above | $-CH_2CH_3$ |
| 886 | Same as above | $-C(=O)-CH_3$ |
| 887 | Same as above | $-CH_2-Ph$ |
| 888 | Same as above | $-C(=O)-Ph$ |
| 889 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 890 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 891 |  | $-CH_3$ |
| 892 | Same as above | $-CH_2CH_3$ |
| 893 | Same as above | $-C(=O)-CH_3$ |
| 894 | Same as above | $-CH_2-Ph$ |
| 895 | Same as above | $-C(=O)-Ph$ |
| 896 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 897 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 898 |  | $-CH_3$ |
| 899 | Same as above | $-CH_2CH_3$ |
| 900 | Same as above | $-C(=O)-CH_3$ |
| 901 | Same as above | $-CH_2-Ph$ |
| 902 | Same as above | $-C(=O)-Ph$ |
| 903 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 904 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 905 |  | $-CH_3$ |
| 906 | Same as above | $-CH_2CH_3$ |
| 907 | Same as above | $-C(=O)-CH_3$ |
| 908 | Same as above | $-CH_2-Ph$ |
| 909 | Same as above | $-C(=O)-Ph$ |
| 910 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 911 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 912 |  | $-CH_3$ |
| 913 | Same as above | $-CH_2CH_3$ |

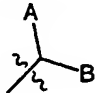
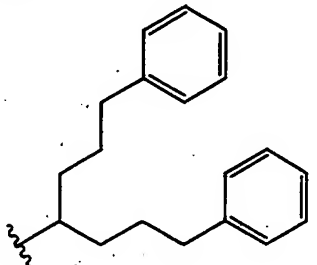
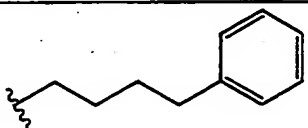
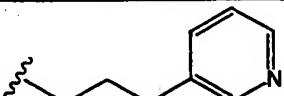
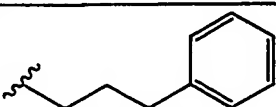
| Cmpd # |  | $-(G)_x-D$ |
|--------|-----------------------------------------------------------------------------------|--------------------|
| 914 | Same as above | $-C(=O)-CH_3$ |
| 915 | Same as above | $-CH_2-Ph$ |
| 916 | Same as above | $-C(=O)-Ph$ |
| 917 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 918 | Same as above | $-C(=O)-C(=O)-Ph$ |

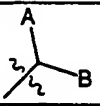
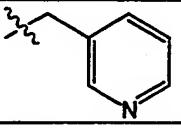
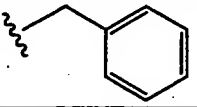
Compounds 919-967 have the formula:



5 the table below , with the individual variables defined in

| Cmpd # |  | $-(G)_x-D$ |
|--------|-------------------------------------------------------------------------------------|--------------------|
| 919 |  | $-CH_3$ |
| 920 | Same as above | $-CH_2CH_3$ |
| 921 | Same as above | $-C(=O)-CH_3$ |
| 922 | Same as above | $-CH_2-Ph$ |
| 923 | Same as above | $-C(=O)-Ph$ |
| 924 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 925 | Same as above | $-C(=O)-C(=O)-Ph$ |

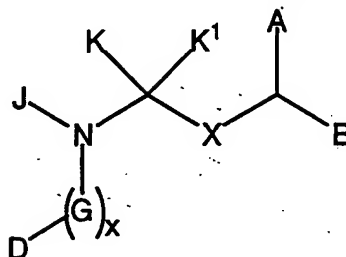
| Cmpd # |  | -(G) _x -D |
|--------|-------------------------------------------------------------------------------------|----------------------------------|
| 926 |  | -CH ₃ |
| 927 | Same as above | -CH ₂ CH ₃ |
| 928 | Same as above | -C(=O)-CH ₃ |
| 929 | Same as above | -CH ₂ -Ph |
| 930 | Same as above | -C(=O)-Ph |
| 931 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 932 | Same as above | -C(=O)-C(=O)-Ph |
| 933 |  | -CH ₃ |
| 934 | Same as above | -CH ₂ CH ₃ |
| 935 | Same as above | -C(=O)-CH ₃ |
| 936 | Same as above | -CH ₂ -Ph |
| 937 | Same as above | -C(=O)-Ph |
| 938 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 939 | Same as above | -C(=O)-C(=O)-Ph |
| 940 |  | -CH ₃ |
| 941 | Same as above | -CH ₂ CH ₃ |
| 942 | Same as above | -C(=O)-CH ₃ |
| 943 | Same as above | -CH ₂ -Ph |
| 944 | Same as above | -C(=O)-Ph |
| 945 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 946 | Same as above | -C(=O)-C(=O)-Ph |
| 947 |  | -CH ₃ |
| 948 | Same as above | -CH ₂ CH ₃ |
| 949 | Same as above | -C(=O)-CH ₃ |
| 950 | Same as above | -CH ₂ -Ph |
| 951 | Same as above | -C(=O)-Ph |
| 952 | Same as above | -C(=O)-O-CH ₂ -Ph |
| 953 | Same as above | -C(=O)-C(=O)-Ph |

| Cmpd # |  | $-(G)_x-D$ |
|--------|-----------------------------------------------------------------------------------|--------------------|
| 954 |  | $-CH_3$ |
| 955 | Same as above | $-CH_2CH_3$ |
| 956 | Same as above | $-C(=O)-CH_3$ |
| 957 | Same as above | $-CH_2-Ph$ |
| 958 | Same as above | $-C(=O)-Ph$ |
| 959 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 960 | Same as above | $-C(=O)-C(=O)-Ph$ |
| 961 |  | $-CH_3$ |
| 962 | Same as above | $-CH_2CH_3$ |
| 963 | Same as above | $-C(=O)-CH_3$ |
| 964 | Same as above | $-CH_2-Ph$ |
| 965 | Same as above | $-C(=O)-Ph$ |
| 966 | Same as above | $-C(=O)-O-CH_2-Ph$ |
| 967 | Same as above | $-C(=O)-C(=O)-Ph$ |

While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products, processes and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific embodiments which have been presented by way of example.

CLAIMS

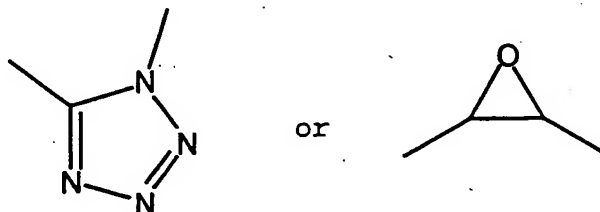
1. A compound having formula (I):



(I)

and pharmaceutically acceptable derivatives thereof,
wherein:

X is selected from $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{C}(\text{OH})\text{CH}_2-$,
 $-\text{CH}_2\text{C}(\text{OH})-$, $=\text{C}(\text{F})\text{CH}_2-$, $-\text{C}(\text{F})=\text{CH}_2-$, $-\text{NHC}(\text{O})-$, $-\text{P}(\text{O})(\text{OH})\text{CH}_2-$,
 $-\text{CH}_2\text{SO}_2-$, $-\text{C}(\text{S})\text{NR}^1-$, $-\text{C}(\text{O})\text{CH}_2\text{CH}(\text{OH})-$, $-\text{C}(\text{OH})\text{CF}_2-$,
 $-\text{C}(\text{O})\text{CF}_2-$, $-\text{CH}(\text{F})\text{CH}_2-$, $-\text{C}(\text{F})_2\text{CH}_2-$,



A, B and R^1 are independently E, $(\text{C}_1-\text{C}_{10})$ -straight or
branched alkyl, $(\text{C}_2-\text{C}_{10})$ -straight or branched alkenyl or
alkynyl, or (C_5-C_7) -cycloalkyl or cycloalkenyl; wherein 1
or 2 hydrogen atoms in said alkyl, alkenyl or alkynyl are
optionally and independently replaced with E,
 (C_5-C_7) -cycloalkyl or cycloalkenyl; and wherein 1 to 2 of
the $-\text{CH}_2-$ groups in said alkyl, alkenyl, or alkynyl groups
is optionally and independently replaced by $-\text{O}-$, $-\text{S}-$,
 $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $=\text{N}-$, $-\text{N}=$ or $-\text{N}(\text{R}^3)-$;

or, B and R^1 are independently hydrogen;

R^3 is hydrogen, (C_1-C_4) -straight or branched alkyl, (C_3-C_4) -straight or branched alkenyl or alkynyl, or (C_1-C_4) bridging alkyl, wherein a bridge is formed between the nitrogen atom to which said R^3 is bound and any carbon atom of said alkyl, alkenyl or alkynyl to form a ring, and wherein said ring is optionally benzofused;

E is a saturated, partially saturated or unsaturated, or aromatic monocyclic or bicyclic ring system, wherein each ring comprises 5 to 7 ring atoms independently selected from C, N, $N(R^3)$, O, S, $S(O)$, or $S(O)_2$; and wherein no more than 4 ring atoms are selected from N, $N(R^3)$, O, S, $S(O)$, or $S(O)_2$;

wherein 1 to 4 hydrogen atoms in E are optionally and independently replaced with halogen, hydroxyl, hydroxymethyl, nitro, SO_3H , trifluoromethyl, trifluoromethoxy, (C_1-C_6) -straight or branched alkyl, (C_2-C_6) -straight or branched alkenyl, O- $[(C_1-C_6)$ -straight or branched alkyl], O- $[(C_3-C_6)$ -straight or branched alkenyl], $(CH_2)_n-N(R^4)(R^5)$, $(CH_2)_n-NH(R^4)-(CH_2)_n-Z$, $(CH_2)_n-N(R^4-(CH_2)_n-Z)(R^5-(CH_2)_n-Z)$, $(CH_2)_n-Z$, O- $(CH_2)_n-Z$, $(CH_2)_n-O-Z$, S- $(CH_2)_n-Z$, $CH=CH-Z$, 1,2-methylenedioxy, $C(O)OH$, $C(O)O-[(C_1-C_6)$ -straight or branched alkyl], $C(O)O-(CH_2)_n-Z$ or $C(O)-N(R^4)(R^5)$;

each of R^4 and R^5 are independently hydrogen, (C_1-C_6) -straight or branched alkyl, (C_3-C_5) -straight or branched alkenyl, or wherein R^4 and R^5 , when bound to the same nitrogen atom, are taken together with the nitrogen atom to form a 5 or 6 membered ring, wherein said ring optionally contains 1 to 3 additional heteroatoms independently selected from N, $N(R^3)$, O, S, $S(O)$, or

S(O)₂; wherein said alkyl, alkenyl or alkynyl groups in R₄ and R₅ are optionally substituted with Z.

each n is independently 0 to 4;

each Z is independently selected from a saturated, partially saturated or unsaturated, monocyclic or bicyclic ring system, wherein each ring comprises 5 to 7 ring atoms independently selected from C, N, N(R³), O, S, S(O), or S(O)₂; and wherein no more than 4 ring atoms are selected from N, N(R³), O, S, S(O), or S(O)₂;

wherein 1 to 4 hydrogen atoms in Z are optionally and independently replaced with halo, hydroxy, nitro, cyano, C(O)OH, (C₁-C₃)-straight or branched alkyl, O-(C₁-C₃)-straight or branched alkyl, C(O)O-[(C₁-C₃)-straight or branched alkyl], amino, NH[(C₁-C₃)-straight or branched alkyl], or N-[(C₁-C₃)-straight or branched alkyl]₂;

J is H, methyl, ethyl or benzyl;

K and K¹ are independently selected from (C₁-C₆)-straight or branched alkyl, (C₂-C₆)-straight or branched alkenyl or alkynyl, or cyclohexylmethyl, wherein 1 to 2 hydrogen atoms in said alkyl, alkenyl or alkynyl is optionally and independently replaced with E;

wherein K and K¹ are independently and optionally substituted with up to 3 substituents selected from halogen, OH, O-(C₁-C₆)-alkyl, O-(CH₂)_n-Z, NO₂, C(O)OH, C(O)-O-(C₁-C₆)-alkyl, C(O)NR⁴R⁵, NR⁴R⁵ and (CH₂)_n-Z; or,

J and K, taken together with the nitrogen and carbon atom to which they are respectively bound, form a 5-7 membered heterocyclic ring, optionally containing up to 3 additional heteroatoms selected from N, N(R³), O, S, S(O), or S(O)₂, wherein 1 to 4 hydrogen atoms in said

heterocyclic ring are optionally and independently replaced with (C₁-C₆)-straight or branched alkyl, (C₂-C₆)-straight or branched alkenyl or alkynyl, oxo, hydroxyl or Z; and wherein any -CH₂- group in said alkyl, alkenyl or alkynyl substituent is optionally and independently replaced by -O-, -S-, -S(O)-, -S(O)₂-, =N-, -N=, or -N(R³)-; and wherein said heterocyclic ring is optionally fused with E;

G, when present, is -S(O)₂-, -C(O)-, -S(O)₂-Y-, -C(O)-Y-, -C(O)-C(O)-, or -C(O)-C(O)-Y-;

Y is oxygen, or N(R⁶);

wherein R⁶ is hydrogen, E, (C₁-C₆)-straight or branched alkyl, (C₃-C₆)-straight or branched alkenyl or alkynyl; or wherein R⁶ and D are taken together with the atoms to which they are bound to form a 5 to 7 membered ring system wherein said ring optionally contains 1 to 3 additional heteroatoms independently selected from O, S, N, N(R³), SO, or SO₂; and wherein said ring is optionally benzofused;

D is hydrogen, (C₁-C₇)-straight or branched alkyl, (C₂-C₇)-straight or branched alkenyl or alkynyl, (C₅-C₇)-cycloalkyl or cycloalkenyl optionally substituted with (C₁-C₆)-straight or branched alkyl or (C₂-C₇)-straight or branched alkenyl or alkynyl, [(C₁-C₇)-alkyl]-E, [(C₂-C₇)-alkenyl or alkynyl]-E, or E;

wherein 1 to 2 of the CH₂ groups of said alkyl, alkenyl or alkynyl chains in D is optionally replaced by -O-, -S-, -S(O)-, -S(O)₂-, =N-, -N=, or -N(R³);

provided that when J is hydrogen or G is selected from -S(O)₂-, C(O)C(O)-, SO₂-Y, C(O)-Y, or C(O)C(O)-Y, wherein Y is O; then D is not hydrogen; and

x is 0 or 1.

2. The compound according to claim 1,

wherein:

each of A and B is independently selected from $-\text{CH}_2-\text{CH}_2-\text{E}$ or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{E}$; and

E is a monocyclic or bicyclic aromatic ring system, wherein said ring comprises 5-7 ring atoms independently selected from C, N, $\text{N}(\text{R}^3)$, O, S, $\text{S}(\text{O})$, or $\text{S}(\text{O})_2$, and wherein 1 to 4 ring atoms are independently selected from N, $\text{N}(\text{R}^3)$, O, S, $\text{S}(\text{O})$, or $\text{S}(\text{O})_2$;

wherein 1 to 4 hydrogen atoms in E are optionally and independently replaced with halogen, hydroxyl, hydroxymethyl, nitro, SO_3H , trifluoromethyl, trifluoromethoxy, (C_1-C_6) -straight or branched alkyl, (C_2-C_6) -straight or branched alkenyl, $\text{O}-[(\text{C}_1-\text{C}_6)$ -straight or branched alkyl], $\text{O}-[(\text{C}_3-\text{C}_6)$ -straight or branched alkenyl], $(\text{CH}_2)_n-\text{N}(\text{R}^4)(\text{R}^5)$, $(\text{CH}_2)_n-\text{NH}(\text{R}^4)-(\text{CH}_2)_n-\text{Z}$, $(\text{CH}_2)_n-\text{N}(\text{R}^4-(\text{CH}_2)_n-\text{Z})(\text{R}^5-(\text{CH}_2)_n-\text{Z})$, $(\text{CH}_2)_n-\text{Z}$, $\text{O}-(\text{CH}_2)_n-\text{Z}$, $(\text{CH}_2)_n-\text{O}-\text{Z}$, $\text{S}-(\text{CH}_2)_n-\text{Z}$, $\text{CH}=\text{CH}-\text{Z}$, 1,2-methylenedioxy, $\text{C}(\text{O})\text{OH}$, or $\text{C}(\text{O})-\text{N}(\text{R}^4)(\text{R}^5)$.

3. The compound according to claim 1 or 2,

wherein D is an aromatic monocyclic or bicyclic ring system, wherein each ring comprises 5 to 7 ring atoms independently selected from C, N, $\text{N}(\text{R}^3)$, O, S, $\text{S}(\text{O})$, or $\text{S}(\text{O})_2$; and wherein no more than 4 ring atoms are selected from N, $\text{N}(\text{R}^3)$, O, S, $\text{S}(\text{O})$, or $\text{S}(\text{O})_2$.

4. The compound according to claim 3,

wherein:

D is phenyl; and

x is 1.

5. The compound according to claim 4, wherein G is $-\text{C}(\text{O})\text{C}(\text{O})-$.

6. The compound according to claim 4, wherein G is $-\text{SO}_2-$.

7. The compound according to claim 4, wherein G is $-\text{C}(\text{O})-$.

8. The compound according to claim 4, wherein G is $-\text{C}(\text{O})\text{Y}-$.

9. The compound according to claim 1 or 2, wherein:

x is 0;

D is selected from $(\text{C}_1\text{-C}_5)$ -straight or branched alkyl, or $[(\text{C}_1\text{-C}_3)$ -straight or branched alkyl]-E; and

E is an aromatic monocyclic or bicyclic ring system, wherein in said ring system each ring comprises 5 to 7 ring atoms independently selected from C, N, $\text{N}(\text{R}^3)$, O, S, $\text{S}(\text{O})$, or $\text{S}(\text{O})_2$; and wherein no more than 4 ring atoms are selected from N, $\text{N}(\text{R}^3)$, O, S, $\text{S}(\text{O})$, or $\text{S}(\text{O})_2$.

10. The compound according to claim 9, wherein E is phenyl.

11. The compound according to claim 2, wherein each of A and B is independently selected from $-\text{CH}_2-\text{CH}_2-\text{E}$ or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{E}$; and

E is pyridyl.

12. A composition comprising a compound according to claim 1 and a pharmaceutically effective carrier.

13. The composition according to claim 12, further comprising a neurotrophic factor.

14. The composition according to claim 13, wherein said neurotrophic factor is selected from nerve growth factor (NGF), insulin-like growth factor (IGF-1) and its active truncated derivatives such as gIGF-1 and Des(1-3)IGF-I, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived growth factors (PDGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factors (CNTF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3) and neurotrophin 4/5 (NT-4/5).

15. The composition according to claim 14, wherein said neurotrophic factor is nerve growth factor (NGF).

16. A method for stimulating neuronal regeneration or preventing neurodegeneration in a patient or in an ex vivo nerve cell, comprising the step of

administering to said patient or said nerve cell a compound according to any one of claims 1-12.

17. The method according to claim 16, wherein said compound is administered to a patient and is formulated together with a pharmaceutically suitable carrier into a pharmaceutically acceptable composition.

18. The method according to claim 17, comprising the additional step of administering to said patient a neurotrophic factor either as part of a multiple dosage form together with said compound or as a separate dosage form.

19. The method according to claim 18, wherein said neurotrophic factor is selected from nerve growth factor (NGF), insulin-like growth factor (IGF-1) and its active truncated derivatives such as gIGF-1 and Des(1-3)IGF-I, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived growth factors (PDGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factors (CNTF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3) and neurotrophin 4/5 (NT-4/5).

20. The method according to claim 19, wherein said neurotrophic factor is nerve growth factor (NGF).

21. The method according to claim 16, wherein said method is used to treat a patient suffering from a disease selected from trigeminal neuralgia,

glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, muscle injury, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured, or prolapsed intervertebrae disk syndrome's, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies, such as those caused by lead, dapsone, ticks, or porphyria, other peripheral myelin disorders, Alzheimer's disease, Gullain-Barre syndrome, Parkinson's disease and other Parkinsonian disorders, ALS, Tourette's syndrome, multiple sclerosis, other central myelin disorders, stroke and ischemia associated with stroke, neural paropathy, other neural degenerative diseases, motor neuron diseases, sciatic crush, neuropathy associated with diabetes, spinal cord injuries, facial nerve crush and other trauma, chemotherapy- and other medication-induced neuropathies, and Huntington's disease.

22. The method according to claim 16, wherein said method is used to stimulate neuronal regeneration in an ex vivo nerve cell.

23. The method according to claim 22, comprising the additional step of contacting said ex vivo nerve cell with a neurotrophic factor.

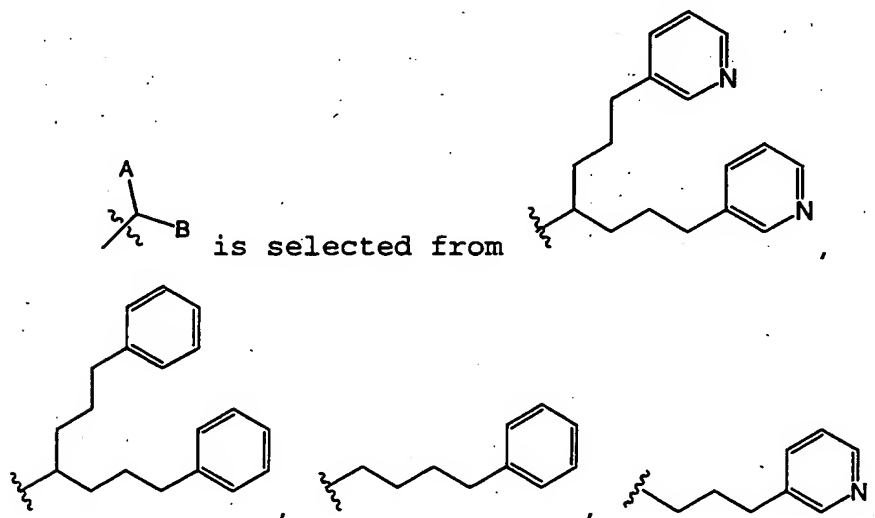
24. The method according to claim 23, wherein said neurotrophic factor is selected from nerve growth factor (NGF), insulin-like growth factor (IGF-1) and its active truncated derivatives such as gIGF-1 and

Des(1-3)IGF-I, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived growth factors (PDGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factors (CNTF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3) and neurotrophin 4/5 (NT-4/5).

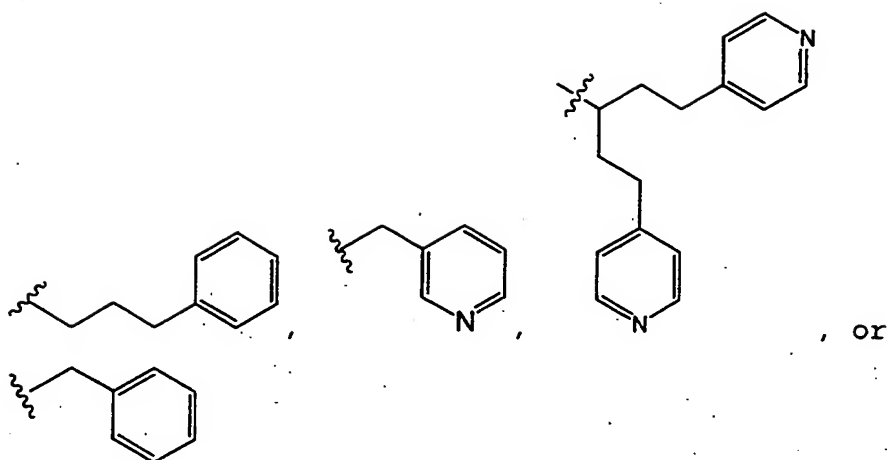
25. The method according to claim 24, wherein said neurotrophic factor is nerve growth factor (NGF).

26. The compound according to claim 1, wherein:

$-(G)_x-D$ is selected from $-CH_3$, $-CH_2CH_3$, $-C(=O)-CH_3$, $-CH_2-Ph$, $-C(=O)-Ph$, $-C(=O)-O-CH_2-Ph$ or $-C(=O)-C(=O)-Ph$, wherein Ph is phenyl; and



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/20491

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/256, 276.4, 264, 265; 548/530, 533, 540; 564/343, 384; 514/333, 343, 341, 423, 422, 408, 427, 332, 327, 330

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| Y | US 5,840,736 A (ZELLE et al.) 24 November 1998, columns 2-5. | 1-12, 16-17, 21-22, 26 |
| X,P — Y,P | US 6,004,993 A (STEINER et al.) 21 December 1999, col. 6, lines 35-45, col. 14, Table I. | 1-10, 12, 16-17, 21-22, 26 — 1-10, 12, 16-17, 21-22, 26 |
| X,P — Y,P | Database CA on STN. Chem. abst. Vol. 132, (Columbus, OH, USA), abstract No. 237375, LI et al. "Preparation of bridged heterocyclic derivatives for treatment of neurological and other disorders" WO 2000016603, 03 March 2000, see entire abstract. | 1-10, 12, 16-17, 21-22, 26 — 1-10, 12, 16-17, 21-22, 26 |

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| * Special categories of cited documents: | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| *A* document defining the general state of the art which is not considered to be of particular relevance | *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| *B* earlier document published on or after the international filing date | *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *A* document member of the same patent family |
| *O* document referring to an oral disclosure, use, exhibition or other means | |
| *P* document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

08 NOVEMBER 2000

Date of mailing of the international search report

15 DEC 2000

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/20491

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| X,P - Y,P | Database CA on STN. Chem. abstr. Vol. 132, 2000, (Columbus, OH, USA), abstract No. 175850, ROSS et al. "Compositions and uses for vision and memory disorders", WO 2000009108, 18 May 2000, see entire abstract. | 1-10, 12, 16-17, 21-22, 26 ---- 1-10, 12, 16-17, 21-22, 26 |
| X - Y | US 5,721,256 A (HAMILTON et al.) 24 February 1998, see entire document, especially col.2, lines 55-67. | 1-10, 12, 16-17, 21-22, 26 --- 1-10, 12, 16-17, 21-22, 26 |
| X - Y | US 5,744,485 A (ZELLE et al.) 28 April 1998, see entire document, especially col. 2, lines 50-67. | 1-10, 12, 16-17, 21-22, 26 ---- 1-10, 12, 16-17, 21-22, 26 |
| X,P - Y,P | US 5,945,441 A (STEINER et al.) 31 August 1999, see entire document especially col. 3 | 1-10, 12, 16-17, 21-22, 26 ---- 1-10, 12, 16-17, 21-22, 26 |
| X - Y | US 5,786,378 A (HAMILTON et al.) 28 July 1998, see entire document especially col.3. | 1-10, 12, 16-17, 21-22, 26 --- 1-10, 12, 16-17, 21-22, 26 |
| X,P - Y,P | US 5,990,131 A (HAMILTON et al.) 23 November 1999, see entire document. | 1-10, 12, 16-17, 21-22, 26 ---- 1-10, 12, 16-17, 21-22, 26 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/20491

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-12,16-17,21-22,26
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/20491

A. CLASSIFICATION OF SUBJECT MATTER: IPC (7):

IPC7 A61K 31/445, 38/18, 31/40, 31/44; C07D 207/06, 211/06, 211/32

A. CLASSIFICATION OF SUBJECT MATTER: US CL :

546/256, 276.4, 264, 265; 548/530, 533, 540; 564/343, 384; 514/333, 343, 341, 423, 422, 408, 427, 332, 327, 330

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

- Group I, claim(s)1-12,16-17,21-22,26 (all in part), drawn to pyrrolidines (J-N-C-K form five membered ring),no other hetero-ring containing (A,B,X all containing no hetero ring), compositions thereof and method of using.
- Group II, claim(s)1-12,16-17,21-22,26 (all in part), drawn to pyrrolidines (J-N-C-K form five membered ring),containing other hetero-ring (A,B,X containing hetero ring), compositions thereof and method of using.
- Group III, claim(s)1-12,16-17,21-22,26 (all in part), drawn to tetrazoles (X is tetrazole) containing no other hetero-ring, compositions thereof and method of using.
- Group IV, claim(s)1-12,16-17,21-22,26 (all in part), drawn to tetrazoles (X is tetrazole) containing other hetero-ring (A,B containing hetero-ring), compositions thereof and method of using.
- Group V, claim(s)1-12,16-17,21-22,26 (all in part), drawn to non-heterocyclic compounds (A, B X, J, D, K all containing no hetero ring), compositions thereof and method of using.
- Group VI, claims 1-12, 16-17, 21-22, 26(all in part), drawn to the remaining compounds.
- Group VII, claims 1-15, 18-20, 23-25, drawn to the method of using the compounds of group I further comprising a neurotrophic factor.
- Group VIII, claims 1-15, 18-20, 23-25, drawn to the method of using the compounds of group II further comprising a neurotrophic factor.
- Group IX, claims 1-15, 18-20, 23-25, drawn to the method of using the compounds of group III further comprising a neurotrophic factor.
- Group X, claims 1-15, 18-20, 23-25, drawn to the method of using the compounds of group IV further comprising a neurotrophic factor.
- Group XI, claims 1-15, 18-20, 23-25, drawn to the method of using the compounds of group V further comprising a neurotrophic factor.
- Group XII, claims 1-15, 18-20, 23-25, drawn to the method of using the compounds of group VI further comprising a neurotrophic factor.

The inventions listed as Groups I-VI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

1. For generic formula I, there is no common core which in the Markush Practice, is a significant structure element (only -C-) shared by all of the alternatives (J,G,D,K,K',X,A,B); See PCT Administrative Instructions Annex B Part I(f)(i)(B)(1)
 2. Further, all alternatives do not belong to a recognized class of chemical compounds in the art to which the invention pertains. Note CA 1999:167033 pyridyl pyrrolidines can be used for hair growth; CA 1999:110352 phenylalkylpyrrolidines can be used for diabetes; CA 97:104598 phenyl pyrrolidines can be used for bradykinin inhibitor
 3. For method of using comprising an additional neurotrophic factor would cause synergistic effect.
- Therefore, no linkage which form a single general inventive concept can be established among the different inventions.

If applicants do not elect, only group I will be searched.